(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050683 A2

(51) International Patent Classification[7]: C07K

(21) International Application Number:
PCT/US2003/038281

(22) International Filing Date: 2 December 2003 (02.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/430,729 2 December 2002 (02.12.2002) US

(71) Applicant *(for all designated States except US)*: **ABGENIX, INC.** [US/US]; 6701 Kaiser Drive, Fremont, CA 94555 (US).

(72) Inventors; and

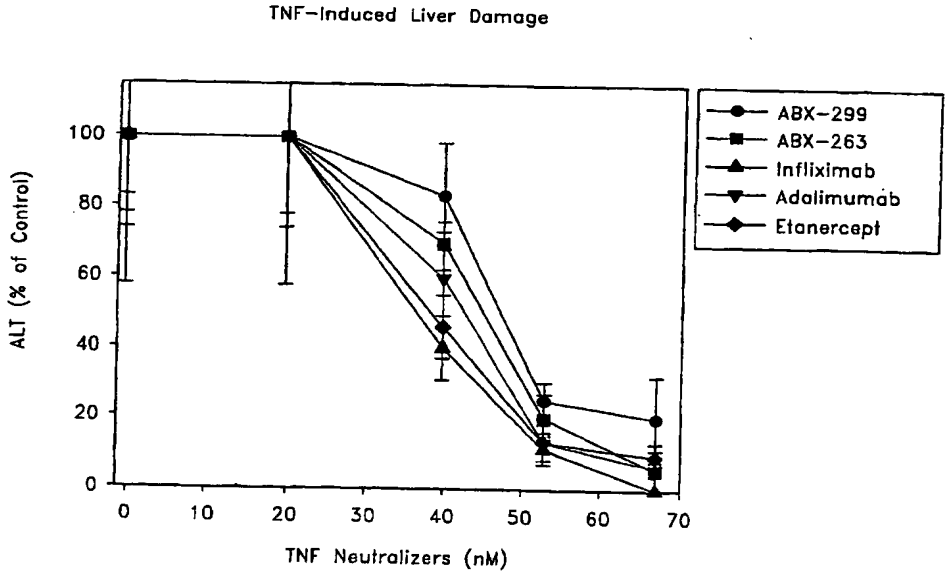
(75) Inventors/Applicants *(for US only)*: **BABCOOK, John, S.** [CA/CA]; 4480 West 12th Avenue, Vancouver, British Columbia V6R 2R2 (CA). **KANG, Jaspal, S.** [CA/CA]; 16727 109 Avenue, Surrey, British Columbia V4N 5H6 (CA). **FOORD, Orit** [US/US]; 712 Cayman Lane, Foster City, CA 94404 (US). **GREEN, Larry** [US/US]; 464 Hill Street, San Francisco, CA 94144 (US). **FENG, Xiao** [US/US]; 135 Red Cedar Lane, Union City, CA 94587 (US). **KLAKAMP, Scott** [US/US]; 1160 Chopin Terrace, #301, Fremont, CA 94538 (US). **HAAK-FRENDSCHO, Mary** [US/US]; 8472 Willow Place, Newark, CA 94560 (US). **RATHANASWAMI, Palaniswami** [CA/CA]; 7878 French Street, Vancouver, British Columbia V6P 4V7 (CA). **PIGOTT, Craig** [CA/CA]; 3941 W. 12th Avenue, Vancouver, British Columbia V6E 1M1 (CA). **LIANG, Meina, L.** [US/US]; 115 Glasgow Circle, Danville, CA 94526 (US). **LEE, Rozanne** [US/US]; 35202 Severn Drive, Newark, CA 94560 (US). **MANCHULENCHO, Kathy** [/]; *. **FAGGIONI, Raffaella** [IT/US]; 634 Windmill Lane, Pleasanton, CA 94566 (US). **SENALDI, Giorgio** [IT/US]; 6534-F Cottonwood Circle, Dublin, CA 94568 (US). **QIAOJUAN, Jane, Su** [/]; *.

(74) Agent: **FULLER, Michael, L.**; Knobbe, Martens, Olson & Bear, LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB,

[Continued on next page]

(54) Title: ANTIBODIES DIRECTED TO TUMOR NECROSIS FACTOR AND USES THEREOF



(57) Abstract: Antibodies directed to the antigen TNFa and uses of such antibodies. In particular, fully human monoclonal antibodies directed to the antigen TNFa. Nucleotide sequences encoding, and amino acid sequences comprising, heavy and light chain immunoglobulin molecules, particularly sequences corresponding to contiguous heavy and light chain sequences spanning the framework regions and/or complementarity determining regions (CDR's), specifically from FR1 through FR4 or CDR1 through CDR3. Hybridomas or other cell lines expressing such immunoglobulin molecules and monoclonal antibodies.

WO 2004/050683 A2

GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANTIBODIES DIRECTED TO TUMOR NECROSIS FACTOR AND USES THEREOF

FIELD

[0001] The present invention relates to antibodies directed to the antigen Tumor Necrosis Factor alpha (hereinafter TNFa) and uses of such antibodies. More specifically, the present invention relates to fully human monoclonal antibodies directed to the antigen TNFa and uses of these antibodies. Aspects of the invention also relate to hybridomas or other cell lines expressing such antibodies. The antibodies herein are useful as diagnostics and as treatments for diseases associated with the activity and/or overproduction of TNFa.

BACKGROUND

[0002] TNFa has been demonstrated to be involved in infectious diseases, immune disorders, autoimmune pathologies, graft vs host disease (GVHD), neoplasia/cancer and cancer-associated cachexia. *See,* Feldman M., 2002 *Nat. Rev. Immunol.*, 2:364. In particular, TNFa levels are dramatically induced in gram negative sepsism, endotoxic shock (*See,* Michie et al., 1989 *Br. J. Surg.* 76:670) Crohn's disease, and rheumatoid arthritis. The implications of TNFa in such a wide variety of indications highlights the importance of developing specific biological therapeutics targeting this inflammatory cytokine.

[0003] Several investigators report the characterization of monoclonal antibodies against TNFa which neutralize its activity *in vitro*. *See,* Liang CM, et al., 1986, *Biochem. Biophys Res. Commun.*, 137:847, and Meager A, et al., 1987 *Hybridoma* 6:305. Some of these antibodies were used to map epitopes of human TNFa and develop enzyme immunoassays and to assist in the purification of recombinant TNFa. *See* Fendly BM, et al., 1987 *Hybridoma*, 6:359; Hirai M, et al., 1987 *J. Immunol Methods*, 96:57; Moller A, et al., 1990 *Cytokine*, 2:162; Bringman TS and Aggarwal BB, 1987, *Hybridoma*, 6:489. Unfortunately, the antibodies generated for these studies would not be useful as therapeutic neutralizing TNFa antibodies for treating human patients since they were derived from non-human species and lack specificity for TNFa.

[0004] Neutralizing antisera or mAbs to TNFa have shown efficacy in non-human mammals by abrogating adverse pathophysiological events and preventing death after lethal challenge in experimental endotoxemia. These effects have been demonstrated in rodent and non-human primate model systems. *See*, Beutler B, et al., 1985 *Science*, 229:869; Tracey KJ, et al., 1987 *Nature*, 330:662; Mathison JC, et al., 1988 *J. Clin. Invest.*, 81:1925; Shimamoto Y, et al., 1988, *Immunol. Lett.*, 17:311; Opal SM, et al., 1990, *J. Infect. Dis.*, 161:1148; Silva AT, et al., 1990, *J. Infect. Dis.*, 162:454; Hinshaw LB, et al., 1990, *Circ. Shock*, 30:279.

[0005] Various forms of neutralizing antibodies currently exist and are reviewed by Feldman. *See*, Feldman M, 2002, *Nat. Rev. Immunol.*, 2:364. As described in this review, a great deal of effort has been expended to create a neutralizing antibody that would yield a therapeutically suitable antibody for chronic administration to humans. Currently, antibody/TNFR fusion (fcIg/TNFR) proteins (Enbrel) have shown some utility, but are challenged by a short half-life in the serum leading to frequent administration (*e.g.*, twice weekly) of the drug. A neutralizing therapeutic antibody to TNFa for chronic treatment would exceed the half-life issue (one injection per 3-4 weeks) as long as the antibody itself was not immunogenic. Others have attempted to create neutralizing antibodies to TNFa which have the desired characteristics of low/no immunogenicity and a half life typical of their endogenous counterparts without success. Examples of such antibodies include mouse/human chimeras, such as Infliximab (cA2 or Remicade), and the humanized antibody CDP571 or Adalimumab (D2E7 or Humira). These represent attempts to create neutralizing therapeutic antibodies which closely resemble their human counterparts.

[0006] Unfortunately, the full potential of these drugs may not be realized due to their inherent potential immunogenicity, compromised half-life and/or reduced avidity/affinity for TNFa. Host immune responses induced by these chimeric antibodies can lead to clearance of the antibodies from the circulation and make repeated administration unsuitable for therapy due to loss of efficacy. These problems ultimately reduce the therapeutic benefit to the patient. Additional problems in scale-up and manufacturing may also be encountered using antibodies or fragments thereof, such as those mentioned above.

[0007] Thus, for the above reasons, there exists a need in the art to provide an alternative to patients in clinically indicated populations where TNFa is responsible for the pathophysiology of a particular disease. Fully human, high affinity, neutralizing monoclonal antibodies, or fragments thereof, for chronic administration provide the desired characteristics of a non-immunogenic therapeutic option with a half-life suitable for less frequent administration.

SUMMARY

[0008] Embodiments of the invention relate to human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and have a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Ser Tyr Asp Met His". Antibodies described herein can also include a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly", a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val", a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 70, and a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 74.

[0009] Further embodiments include human monoclonal antibodies having a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly". Antibodies herein can also include a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Ala Ala Ser Thr Leu Gln Ser", a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Leu Gln His Lys Ser Tyr Pro Leu Thr", a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 72.

[0010] In other embodiments, the invention provides human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly", a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Ala Ala Ser Thr Leu Gln Ser", and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Leu Gln His Lys Ser Tyr Pro Leu Thr".

[0011] Still further embodiments include human monoclonal antibodies having a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Ser Tyr Asp Met His", a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly", and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val".

[0012] In other embodiments the invention includes human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and include a VH3-33 heavy chain gene, or conservative variants thereof. Antibodies described herein can also include an A30VK1 light chain gene.

[0013] Further embodiments of the invention include human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a, wherein the antibodies comprise a heavy chain complementarity determining region 1 (CDR1) corresponding to canonical class 1. The antibodies provided herein can also include a heavy chain complementarity determining region 2 (CDR2) corresponding to canonical class 3, a light chain complementarity determining region 1 (CDR1) corresponding to canonical class 2, a light chain complementarity determining region 2 (CDR2) corresponding to canonical class 1, and a light chain complementarity determining region 3 (CDR3) corresponding to canonical class 1.

[0014] In other embodiments, the invention provides human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and include a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Asn Tyr Met Ser". Antibodies can further include a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly", a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gly

Glu Gly Gly Phe Asp Tyr", and a heavy chain amino acid having the amino acid sequence shown in SEQ ID NO: 50.

[0015] In further embodiments of the invention, human monoclonal antibodies can include a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala", a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Gly Ala Ser Ile Arg Ala Thr", a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gln Gln Tyr Asn Tyr Trp Trp Thr", and a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 52.

[0016] In still further embodiments, the invention includes human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and have a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala", a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Gly Ala Ser Ile Arg Ala Thr", a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gln Gln Tyr Asn Tyr Trp Trp Thr", a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Asn Tyr Met Ser", a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly", and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gly Glu Gly Gly Phe Asp Tyr".

[0017] In other embodiments, the invention provides human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a and have a VH3-53 heavy chain gene, or conservative variant thereof. Antibodies herein can also include an L2VK3 light chain gene.

[0018] In additional embodiments, the invention includes human monoclonal antibodies that specifically bind to Tumor Necrosis Factor-a, wherein the antibodies comprise a heavy chain complementarity determining region 1 (CDR1) corresponding to canonical class 1. The antibodies herein can also include a heavy chain complementarity determining region 2 (CDR2) corresponding to canonical class 1, a light chain complementarity determining region 1 (CDR1) corresponding to canonical class 2, a light chain complementarity determining region 2 (CDR2) corresponding to canonical class 1, and a light chain complementarity determining region 3 (CDR3) corresponding to canonical class 3.

[0019] The invention further provides methods for assaying the level of tumor necrosis factor alpha (TNFa) in a patient sample, comprising contacting an anti-TNFa antibody with a biological sample from a patient, and detecting the level of binding between said antibody and TNFa in said sample. In more specific embodiments, the biological sample is blood.

[0020] In other embodiments the invention provides compositions, including an antibody or functional fragment thereof, and a pharmaceutically acceptable carrier.

[0021] Still further embodiments of the invention include methods of effectively treating an animal suffering from a neoplastic disease, including selecting an animal in need of treatment for a neoplastic disease, and administering to said animal a therapeutically effective dose of a fully human monoclonal antibody that specifically binds to tumor necrosis factor alpha (TNFa).

[0022] Treatable neoplastic diseases can include breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, stomach cancer, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and prostrate cancer.

[0023] Further methods of the invention relate to effectively treating an immuno-mediated inflammatory disease. These methods include selecting an animal in need of treatment for an inflammatory condition, and administering to said animal a therapeutically effective dose of a fully human monoclonal antibody, wherein said antibody specifically binds to tumor necrosis factor alpha (TNFa). Treatable immuno-mediated inflammatory diseases include rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, ankylosing spondylitis and multiple sclerosis.

[0024] Additional embodiments of the invention include methods of inhibiting tumor necrosis factor alpha (TNFa) induced apoptosis in an animal. These methods include selecting an animal in need of treatment for TNFa induced apoptosis, and administering to said animal a therapeutically effective dose of a fully human monoclonal antibody wherein said antibody specifically binds to TNFa.

[0025] Further embodiments of the invention include the use of an antibody of in the preparation of medicament for the treatment of neoplastic disease in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa). Treatable neoplastic diseases can include breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, stomach cancer, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and prostrate cancer.

[0026] Further uses of the antibodies herein can be for the preparation of a medicament for the effective treatment of immuno-mediated inflammatory diseases in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa). Treatable immuno-mediated inflammatory diseases can include rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis.

[0027] In still further embodiments, the antibodies described herein can be used for the preparation of a medicament for the effective treatment of tumor necrosis factor induced apoptosis in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa).

[0028] Embodiments of the invention described herein related to monoclonal antibodies that bind TNFa and affect TNFa function. Other embodiments relate to fully human anti-TNFa antibodies and anti-TNFa antibody preparations with desirable properties from a therapeutic perspective, including strong binding affinity for TNFa, the ability to neutralize TNFa *in vitro* and *in vivo*, and the ability to inhibit TNFa induced apoptosis.

[0029] In a preferred embodiment, antibodies described herein bind to TNFa with very high affinities (Kd). For example a human, rabbit, mouse, chimeric or humanized antibody that is capable of binding TNFa with a Kd less than, but not limited to, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or 10^{-14} M, or any range or value therein. The rabbit antibody R014, described herein, possesses a measured affinity in the 10^{-13} (fM) range. Antibody 299 V.1 and 299 V.2 were shown to possess affinities in the 10^{-13} or low 10^{-12} (M) range. Affinity and/or avidity measurements can be measured by KinExA® and/or BIACORE®, as described herein.

[0030] Accordingly, one embodiment described herein includes isolated antibodies, or fragments of those antibodies, that bind to TNFa. As known in the art, the antibodies can advantageously be, for example, monoclonal, chimeric and/or fully human antibodies. Embodiments of the invention described herein also provide cells for producing these antibodies.

[0031] Another embodiment of the invention is a fully human antibody that binds to TNFa and comprises a heavy chain amino acid sequence having the complementarity determining region (CDR) with one of the sequences shown in Tables 31-34. It is noted that CDR determinations can be readily accomplished by those of ordinary skill in the art. See for example, Kabat et al., *Sequences of Proteins of Immunological Interest,* Fifth Edition, NIH Publication 91-3242, Bethesda MD [1991], vols. 1-3.

[0032] Yet another embodiment is an antibody that binds to TNFa and comprises a light chain amino acid sequence having a CDR comprising one of the sequences shown in Tables 32 and 34. In certain embodiments the antibody is a fully human monoclonal antibody.

[0033] A further embodiment is an antibody that binds to TNFa and comprises a heavy chain amino acid sequence having one of the CDR sequences shown in Tables 31 and 33 and a light chain amino acid sequence having one of the CDR sequences shown in Tables 32 and 34. In certain embodiments the antibody is a fully human monoclonal antibody.

[0034] Another embodiment of the invention is a fully human antibody that binds to other TNFa family members including, but not limited to, TNFß. A further embodiment herein is an antibody that cross-competes for binding to TNFa with the fully human antibodies of the invention.

[0035] It will be appreciated that embodiments of the invention are not limited to any particular form of an antibody or method of generation or production. For example, the anti-TNFa antibody may be a full-length antibody (*e.g.*, having an intact human Fc region) or an antibody fragment (*e.g.*, a Fab, Fab' or $F(ab')_2$). In addition, the antibody may be manufactured from a

hybridoma that secretes the antibody, or from a recombinantly produced cell that has been transformed or transfected with a gene or genes encoding the antibody.

[0036] Other embodiments of the invention include isolated nucleic acid molecules encoding any of the antibodies described herein, vectors having an isolated nucleic acid molecules encoding anti-TNFa antibodies or a host cell transformed with any of such nucleic acid molecules. In addition, one embodiment of the invention is a method of producing an anti-TNFa antibody by culturing host cells under conditions wherein a nucleic acid molecule is expressed to produce the antibody followed by recovering the antibody.

[0037] A further embodiment herein includes a method of producing high affinity antibodies to TNFa by immunizing a mammal with human TNFa, or a fragment thereof, and one or more orthologous sequences or fragments thereof.

[0038] Other embodiments are based upon the generation and identification of isolated antibodies that bind specifically to TNFa. TNFa is expressed at elevated levels in neoplastic diseases, such as tumors, and other inflammatory diseases. Inhibition of the biological activity of TNFa can prevent inflammation and other desired effects, including TNFa induced apoptosis.

[0039] Another embodiment of the invention includes a method of diagnosing diseases or conditions in which an antibody prepared as described herein is utilized to detect the level of TNFa in a patient sample. In one embodiment, the patient sample is blood or blood serum. In further embodiments, methods for the identification of risk factors, diagnosis of disease, and staging of disease is presented which involves the identification of the overexpression of TNFa using anti-TNFa antibodies.

[0040] Another embodiment of the invention includes a method for diagnosing a condition associated with the expression of TNFa in a cell by contacting the cell with an anti-TNFa antibody, and thereafter detecting the presence of TNFa. Preferred conditions include, but are not limited to, neoplastic diseases including, without limitation, tumors, cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer. In another embodiment, an anti-TNFa antibody can be used to diagnose an inflammatory condition including, but is not limited to, atherosclerosis, restenosis, autoimmune disease, immuno-mediated inflammatory diseases (IMIDs) including but not limited to rheumatoid arthritis, psoriasis, uveitis (*e.g.*, childhood and seronegative), lupus and other diseases mediated by immune complexes such as pemphigus and glomerulonephritis, congential hyperthyroidism (CH), delayed type hypersensitivity (DTH) such as contact hypersensitivity, sarcoidosis, Behcet's disease, chronic arthritis, psoriatic arthritis, ankylosing spondylitis, adult still disease, primary Sjögren's disease, scleroderma, giant cell arteritis, SAPHO syndrome, primary biliary cirrhosis (PBC), sarcoidosis, myelodysplastic syndromes, Wegener's syndrome and other vasculitis, hematologic malignancies, cochleovestibular disorders, macrophage activation syndrome, asthma, interstitial lung disease, Hepatitis C, pulmonary fibrosis, ovulation induction,

myelodysplastic syndromes, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis. Other conditions the antibodies can diagnose are disclosed in U.S. Patent No. 6,090,382 to Salfeld et al., and U.S. Patent No. 5,436,154 to Barbanti, et al..

[0041] In another embodiment, the invention includes an assay kit for detecting TNFa and TNFa family members in mammalian tissues or cells to screen for neoplastic diseases or inflammatory conditions. The kit includes an antibody that binds to TNFa and a means for indicating the reaction of the antibody with TNFa, if present. Preferably the antibody is a monoclonal antibody. In one embodiment, the antibody that binds TNFa is labeled. In another embodiment the antibody is an unlabeled first antibody and the kit further includes a means for detecting the first antibody. In one embodiment, the means includes a labeled second antibody that is an anti-immunoglobulin. Preferably the antibody is labeled with a marker selected from the group consisting of a fluorochrome, an enzyme, a radionuclide and a radiopaque material.

[0042] Other embodiments of the invention include pharmaceutical compositions having an effective amount of an anti-TNFa antibody in admixture with a pharmaceutically acceptable carrier or diluent. In yet other embodiments, the anti-TNFa antibody, or a fragment thereof, is conjugated to a therapeutic agent. The therapeutic agent can be, for example, a toxin or a radioisotope. Preferably, such antibodies can be used for the treatment of diseases, including for example, tumors, cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer, as well as other inflammatory conditions including but not limited to, atherosclerosis, restenosis, autoimmune disease, immuno-mediated inflammatory diseases (IMIDs) including but not limited to rheumatoid arthritis, psoriasis, uveitis (*e.g.,* childhood and seronegative), lupus and other diseases mediated by immune complexes such as pemphigus and glomerulonephritis, congential hyperthyroidism (CH), delayed type hypersensitivity (DTH) such as contact hypersensitivity, sarcoidosis, Behcet's disease, chronic arthritis, psoriatic arthritis, ankylosing spondylitis, adult still disease, primary Sjögren's disease, scleroderma, giant cell arteritis, SAPHO syndrome, primary biliary cirrhosis (PBC), sarcoidosis, myelodysplastic syndromes, Wegener's syndrome and other vasculitis, hematologic malignancies, cochleovestibular disorders, macrophage activation syndrome, asthma, interstitial lung disease, Hepatitis C, pulmonary fibrosis, ovulation inductionmyelodysplastic syndromes, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis. Other conditions the antibodies can treat are disclosed in U.S. Patent No. 6,090,382 to Salfeld et al., and U.S. Patent No. 5,436,154 to Barbanti, et al.

[0043] Yet another embodiment includes methods for treating diseases or conditions associated with the expression of TNFa in a patient, by administering to the patient an effective amount of an anti-TNFa antibody. The method can be performed *in vivo* and the patient is preferably a human patient. In a preferred embodiment, the method concerns the treatment of tumors, tumors, cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney,

colon, colorectal, thyroid, pancreatic, prostate and bladder cancer. In another embodiment, the inflammatory condition includes, but is not limited to, atherosclerosis, restenosis, autoimmune disease, immuno-mediated inflammatory diseases (IMIDs) including but not limited to rheumatoid arthritis, psoriasis, uveitis (*e.g.*, childhood and seronegative), lupus and other diseases mediated by immune complexes such as pemphigus and glomerulonephritis, congential hyperthyroidism (CH), delayed type hypersensitivity (DTH) such as contact hypersensitivity, sarcoidosis, Behcet's disease, chronic arthritis, psoriatic arthritis, ankylosing spondylitis, adult still disease, primary Sjögren's disease, scleroderma, giant cell arteritis, SAPHO syndrome, primary biliary cirrhosis (PBC), sarcoidosis, myelodysplastic syndromes, Wegener's syndrome and other vasculitis, hematologic malignancies, cochleovestibular disorders, macrophage activation syndrome, asthma, interstitial lung disease, Hepatitis C, pulmonary fibrosis, ovulation induction, myelodysplastic syndromes, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis. Other conditions the antibodies can treat are disclosed in U.S. Patent No. 6,090,382 to Salfeld et al., and U.S. Patent No. 5,436,154 to Barbanti, et al.

[0044] In another embodiment, the invention provides an article of manufacture including a container. The container includes a composition containing an anti-TNFa antibody, and a package insert or label indicating that the composition can be used to treat neoplastic or inflammatory diseases characterized by the overexpression of TNFa.

[0045] In some embodiments, the anti-TNFa antibody is administered to a patient, followed by administration of a clearing agent to remove excess circulating antibody from the blood.

[0046] In some embodiments, anti-TNFa antibodies can be modified to enhance their capability of fixing complement and participating in complement-dependent cytotoxicity (CDC). In one embodiment, anti-TNFa antibodies can be modified, such as by an amino acid substitution, to alter their clearance from the body. Alternatively, some other amino acid substitutions may slow clearance of the antibody from the body.

[0047] Yet another embodiment is the use of an anti-TNFa antibody in the preparation of a medicament for the treatment of diseases such as neoplastic diseases and inflammatory conditions. In one embodiment, the neoplastic diseases include tumors and cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer. In another embodiment, the inflammatory condition includes, but is not limited to, atherosclerosis, restenosis, autoimmune disease, immuno-mediated inflammatory diseases (IMIDs) including but not limited to rheumatoid arthritis, psoriasis, uveitis (*e.g.*, childhood and seronegative), lupus and other diseases mediated by immune complexes such as pemphigus and glomerulonephritis, congential hyperthyroidism (CH), delayed type hypersensitivity (DTH) such as contact hypersensitivity, sarcoidosis, Behcet's disease, chronic arthritis, psoriatic arthritis, ankylosing spondylitis, adult still disease, primary Sjögren's disease, scleroderma, giant cell

arteritis, SAPHO syndrome, primary biliary cirrhosis (PBC), sarcoidosis, myelodysplastic syndromes, Wegener's syndrome and other vasculitis, hematologic malignancies, cochleovestibular disorders, macrophage activation syndrome, asthma, interstitial lung disease, Hepatitis C, pulmonary fibrosis, ovulation induction, myelodysplastic syndromes, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis. Other conditions the antibodies can treat are disclosed in U.S. Patent No. 6,090,382 to Salfeld et al., and U.S. Patent No. 5,436,154 to Barbanti, et al..

BRIEF DESCRIPTION OF THE DRAWINGS

[0048] Fig. 1 is a bar graph which illustrates the effect that various hybridoma derived, human anti-TNFa binding antibodies have on neutralizing TNFa induced cell apoptosis in human WM 266 cells. The graph shows caspase activity as a measure of TNFa induced apoptosis.

[0049] Fig. 2 is a point graph that compares the anti-TNFa limited antigen binding between antibodies in B-cell culture supernatants to that of a control antibody (4.17 IgG2) over a concentration range. The triangles represent the B-cell culture supernatant clones, and the blocks represent Bar Antibody (4.17 IgG2). B-cell culture supernatants clones with points above the bar antibody curve are ranked as having potentially higher affinity.

[0050] Fig. 3 is a representative bar graph that compares the effectiveness of various XENOMAX® B-cell culture supernatants at inhibiting TNFa induced cell apoptosis in human MCF-7 cells.

[0051] Fig. 4 is a representative point graph that shows calculated potency comparisons for neutralization of TNFa induced apoptosis on human MCF-7 cells by XENOMAX® B-cell culture supernatants. The triangles represent the potency of B-cell culture supernatants, while the squares represent the potency of a bar control, 3.2 IgG2.

[0052] Fig. 5 is a line graph of anti-TNF reagents binding E. coli expressed soluble human TNF by ELISA.

[0053] Fig. 6 is a line graph of anti-TNF reagents binding and cross-reacting to E. coli expressed soluble cynomolgous macaque monkey TNF by ELISA.

[0054] Fig. 7 is a representative line graph showing an example of neutralizing anti-TNFa antibody titration curves used to generate IC_{50} values. Anti-TNFa reagents were pre-incubated with 100 pg/ml of TNFa for 1 hour at 37°C. Neutralization was assayed using MCF-7 cells and detected as a ratio of propidium iodide and Heochst 33342 staining.

[0055] Fig. 8 is a representative line graph showing an example of neutralizing anti-TNFa reagents titration curves used to generate IC_{50} values. Anti-TNFa antibodies were pre-incubated with 100 pg/ml of TNFa for 18 hours at 37°C. Neutralization was assayed using MCF-7 cells and detected as a ratio of propidium iodide and Heochst 33342 staining.

[0056] Fig. 9 is a bar graph that shows the average IC_{50} values for anti-TNFa neutralization. Neutralization and IC_{50} calculations were performed as described in the brief description of Figure 8.

[0057] Fig. 10 is a bar graph that shows the average IC_{50} values for anti-TNFa neutralization. Neutralization was performed on human WM266 cells and caspase activity was measured as an indication of TNFa induced apoptosis. Antibody IC_{50} calculations were performed as described in the brief description of Figure 7.

[0058] Fig. 11 is a line graph representing a whole blood assay for the inhibition of IL-8 induction by TNF, measured by ELISA. Titration curves were used to generate IC_{50} values.

[0059] Fig. 12 is a representative line graph of the *in-vivo* inhibition of TNFa induced hepatic failure using anti-TNF reagents. Liver injury induced by TNFa and D-GalN was assessed by measuring serum enzyme activities of alanine aminotransferase (ALT). Titration curves were used to generate IC_{50} values.

[0060] Fig. 13 is a representative line graph of the *in-vivo* inhibition of TNFa induced IL-6 using anti-TNF reagents and measured by ELISA. Titration curves were used to generate IC_{50} values

DETAILED DESCRIPTION

[0061] Embodiments of the invention described herein relate to monoclonal antibodies that bind to TNFa. In some embodiments, the antibodies bind to TNFa and affect TNFa function. Other embodiments provide fully human anti-TNFa antibodies and anti-TNFa antibody preparations with desirable properties from a therapeutic perspective, including strong binding affinity for TNFa, the ability to neutralize TNFa *in vitro*, the ability to inhibit TNFa-induced hepatic injury *in vivo*, and the ability to inhibit TNFa-induced IL-6 production *in vivo*.

[0062] Accordingly, embodiments of the invention include isolated antibodies, or fragments of those antibodies, that bind to TNFa. As known in the art, the antibodies can advantageously be fully human monoclonal antibodies. Embodiments of the invention also provide cells for producing these antibodies.

[0063] In addition, embodiments of the invention provide for using these antibodies as a diagnostic tool or for treatment of a disease. For example, embodiments of the invention provide methods and antibodies for inhibiting expression of TNFa associated with infectious diseases, immune disorders, autoimmune pathologies, graft vs. host disease (GVHD), neoplasia, cancer associated cachexia, gram negative sepsism, endotoxic shock, Crohn's disease, and rheumatoid arthritis. Preferably, the antibodies are used to treat cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer, as well as other inflammatory conditions, including, but not limited to, rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, organ transplants, restenosis and

autoimmune diseases. In association with such treatment, articles of manufacture including antibodies as described herein are provided. Additionally, an assay kit having antibodies as described herein is provided to screen for tumors and inflammatory conditions.

[0064] Additionally, the nucleic acids described herein, and fragments and variants thereof, may be used, by way of nonlimiting example, (a) to direct the biosynthesis of the corresponding encoded proteins, polypeptides, fragments and variants as recombinant or heterologous gene products, (b) as probes for detection and quantification of the nucleic acids disclosed herein, (c) as sequence templates for preparing antisense molecules, and the like. Such uses are described more fully in the following disclosure.

[0065] Furthermore, the proteins and polypeptides described herein, and fragments and variants thereof, may be used in ways that include (a) serving as an immunogen to stimulate the production of an anti-TNFa antibody, (b) a capture antigen in an immunogenic assay for such an antibody, (c) as a target for screening for substances that bind to a TNFa polypeptide described herein, and (d) a target for a TNFa specific antibody such that treatment with the antibody affects the molecular and/or cellular function mediated by the target.

[0066] Further embodiments, features, and the like regarding the anti-TNFa antibodies are provided in additional detail below.

Sequence Listing

[0067] The heavy chain and light chain variable region nucleotide and amino acid sequences of representative human anti-TNFa antibodies are provided in the sequence listing, the contents of which are summarized in Table 1 below.

Table 1

mAb ID No.:	Sequence	SEQ ID NO:
2	Nucleotide sequence encoding the variable region of the heavy chain	1
	Amino acid sequence encoding the variable region of the heavy chain	2
	Nucleotide sequence encoding the variable region of the light chain	3
	Amino acid sequence encoding the variable region of the light chain	4
15	Nucleotide sequence encoding the variable region of the heavy chain	5
	Amino acid sequence encoding the variable region of the heavy chain	6
	Nucleotide sequence encoding the variable region of the light chain	7
	Amino acid sequence encoding the variable region of the light chain	8
25	Nucleotide sequence encoding the variable region of the heavy chain	9
	Amino acid sequence encoding the variable region of the heavy chain	10

	Nucleotide sequence encoding the variable region of the light chain	11
	Amino acid sequence encoding the variable region of the light chain	12
28	Nucleotide sequence encoding the variable region of the heavy chain	13
	Amino acid sequence encoding the variable region of the heavy chain	14
	Nucleotide sequence encoding the variable region of the light chain	15
	Amino acid sequence encoding the variable region of the light chain	16
70k/69g	Nucleotide sequence encoding the variable region of the heavy chain	17
	Amino acid sequence encoding the variable region of the heavy chain	18
	Nucleotide sequence encoding the variable region of the light chain	19
	Amino acid sequence encoding the variable region of the light chain	20
95	Nucleotide sequence encoding the variable region of the heavy chain	21
	Amino acid sequence encoding the variable region of the heavy chain	22
	Nucleotide sequence encoding the variable region of the light chain	23
	Amino acid sequence encoding the variable region of the light chain	24
123	Nucleotide sequence encoding the variable region of the heavy chain	25
	Amino acid sequence encoding the variable region of the heavy chain	26
	Nucleotide sequence encoding the variable region of the light chain	27
	Amino acid sequence encoding the variable region of the light chain	28
131	Nucleotide sequence encoding the variable region of the heavy chain	29
	Amino acid sequence encoding the variable region of the heavy chain	30
	Nucleotide sequence encoding the variable region of the light chain	31
	Amino acid sequence encoding the variable region of the light chain	32
145k/ 140g	Nucleotide sequence encoding the variable region of the heavy chain	33
	Amino acid sequence encoding the variable region of the heavy chain	34
	Nucleotide sequence encoding the variable region of the light chain	35
	Amino acid sequence encoding the variable region of the light chain	36
148	Nucleotide sequence encoding the variable region of the heavy chain	37
	Amino acid sequence encoding the variable region of the heavy chain	38
	Nucleotide sequence encoding the variable region of the light chain	39
	Amino acid sequence encoding the variable region of the light chain	40
234	Nucleotide sequence encoding the variable region of the heavy chain	41
	Amino acid sequence encoding the variable region of the heavy chain	42
	Nucleotide sequence encoding the variable region of the light chain	43
	Amino acid sequence encoding the variable region of the light chain	44

250	Nucleotide sequence encoding the variable region of the heavy chain	45
	Amino acid sequence encoding the variable region of the heavy chain	46
	Nucleotide sequence encoding the variable region of the light chain	47
	Amino acid sequence encoding the variable region of the light chain	48
263	Nucleotide sequence encoding the variable region of the heavy chain	49
	Amino acid sequence encoding the variable region of the heavy chain	50
	Nucleotide sequence encoding the variable region of the light chain	51
	Amino acid sequence encoding the variable region of the light chain	52
269	Nucleotide sequence encoding the variable region of the heavy chain	53
	Amino acid sequence encoding the variable region of the heavy chain	54
	Nucleotide sequence encoding the variable region of the light chain	55
	Amino acid sequence encoding the variable region of the light chain	56
280	Nucleotide sequence encoding the variable region of the heavy chain	57
	Amino acid sequence encoding the variable region of the heavy chain	58
	Nucleotide sequence encoding the variable region of the light chain	59
	Amino acid sequence encoding the variable region of the light chain	60
282	Nucleotide sequence encoding the variable region of the heavy chain	61
	Amino acid sequence encoding the variable region of the heavy chain	62
	Nucleotide sequence encoding the variable region of the light chain	63
	Amino acid sequence encoding the variable region of the light chain	64
291	Nucleotide sequence encoding the variable region of the heavy chain	65
	Amino acid sequence encoding the variable region of the heavy chain	66
	Nucleotide sequence encoding the variable region of the light chain	67
	Amino acid sequence encoding the variable region of the light chain	68
299v1	Nucleotide sequence encoding the variable region of the heavy chain	69
	Amino acid sequence encoding the variable region of the heavy chain	70
	Nucleotide sequence encoding the variable region of the light chain	71
	Amino acid sequence encoding the variable region of the light chain	72
299v2	Nucleotide sequence encoding the variable region of the heavy chain	73
	Amino acid sequence encoding the variable region of the heavy chain	74
	Nucleotide sequence encoding the variable region of the light chain	71
	Amino acid sequence encoding the variable region of the light chain	72
313	Nucleotide sequence encoding the variable region of the heavy chain	75
	Amino acid sequence encoding the variable region of the heavy chain	76
	Nucleotide sequence encoding the variable region of the light chain	77

	Amino acid sequence encoding the variable region of the light chain	78
R014	Nucleotide sequence encoding the variable region of the heavy chain	79
	Amino acid sequence encoding the variable region of the heavy chain	80
	Nucleotide sequence encoding the variable region of the light chain	81
	Amino acid sequence encoding the variable region of the light chain	82
1.1	Nucleotide sequence encoding the variable region of the heavy chain	83
	Amino acid sequence encoding the variable region of the heavy chain	84
	Nucleotide sequence encoding the variable region of the light chain	85
	Amino acid sequence encoding the variable region of the light chain	86
2.1	Nucleotide sequence encoding the variable region of the heavy chain	87
	Amino acid sequence encoding the variable region of the heavy chain	88
	Nucleotide sequence encoding the variable region of the light chain	89
	Amino acid sequence encoding the variable region of the light chain	90
2.2	Nucleotide sequence encoding the variable region of the heavy chain	91
	Amino acid sequence encoding the variable region of the heavy chain	92
	Nucleotide sequence encoding the variable region of the light chain	93
	Amino acid sequence encoding the variable region of the light chain	94
2.3	Nucleotide sequence encoding the variable region of the heavy chain	95
	Amino acid sequence encoding the variable region of the heavy chain	96
	Nucleotide sequence encoding the variable region of the light chain	97
	Amino acid sequence encoding the variable region of the light chain	98
2.4	Nucleotide sequence encoding the variable region of the heavy chain	99
	Amino acid sequence encoding the variable region of the heavy chain	100
	Nucleotide sequence encoding the variable region of the light chain	101
	Amino acid sequence encoding the variable region of the light chain	102
2.5	Nucleotide sequence encoding the variable region of the heavy chain	103
	Amino acid sequence encoding the variable region of the heavy chain	104
	Nucleotide sequence encoding the variable region of the light chain	105
	Amino acid sequence encoding the variable region of the light chain	106
2.6	Nucleotide sequence encoding the variable region of the heavy chain	107
	Amino acid sequence encoding the variable region of the heavy chain	108
	Nucleotide sequence encoding the variable region of the light chain	109
	Amino acid sequence encoding the variable region of the light chain	110
2.7	Nucleotide sequence encoding the variable region of the heavy chain	111
	Amino acid sequence encoding the variable region of the heavy chain	112

	Nucleotide sequence encoding the variable region of the light chain	113
	Amino acid sequence encoding the variable region of the light chain	114
2.8	Nucleotide sequence encoding the variable region of the heavy chain	115
	Amino acid sequence encoding the variable region of the heavy chain	116
	Nucleotide sequence encoding the variable region of the light chain	117
	Amino acid sequence encoding the variable region of the light chain	118
2.9	Nucleotide sequence encoding the variable region of the heavy chain	119
	Amino acid sequence encoding the variable region of the heavy chain	120
	Nucleotide sequence encoding the variable region of the light chain	121
	Amino acid sequence encoding the variable region of the light chain	122
2.10	Nucleotide sequence encoding the variable region of the heavy chain	123
	Amino acid sequence encoding the variable region of the heavy chain	124
	Nucleotide sequence encoding the variable region of the light chain	125
	Amino acid sequence encoding the variable region of the light chain	126
2.13	Nucleotide sequence encoding the variable region of the heavy chain	127
	Amino acid sequence encoding the variable region of the heavy chain	128
	Nucleotide sequence encoding the variable region of the light chain	129
	Amino acid sequence encoding the variable region of the light chain	130
2.14	Nucleotide sequence encoding the variable region of the heavy chain	131
	Amino acid sequence encoding the variable region of the heavy chain	132
	Nucleotide sequence encoding the variable region of the light chain	133
	Amino acid sequence encoding the variable region of the light chain	134
2.15	Nucleotide sequence encoding the variable region of the heavy chain	135
	Amino acid sequence encoding the variable region of the heavy chain	136
	Nucleotide sequence encoding the variable region of the light chain	137
	Amino acid sequence encoding the variable region of the light chain	138
2.16	Nucleotide sequence encoding the variable region of the heavy chain	139
	Amino acid sequence encoding the variable region of the heavy chain	140
	Nucleotide sequence encoding the variable region of the light chain	141
	Amino acid sequence encoding the variable region of the light chain	142
2.17	Nucleotide sequence encoding the variable region of the heavy chain	143
	Amino acid sequence encoding the variable region of the heavy chain	144
	Nucleotide sequence encoding the variable region of the light chain	145
	Amino acid sequence encoding the variable region of the light chain	146
2.18	Nucleotide sequence encoding the variable region of the heavy chain	147

	Amino acid sequence encoding the variable region of the heavy chain	148
	Nucleotide sequence encoding the variable region of the light chain	149
	Amino acid sequence encoding the variable region of the light chain	150
2.19	Nucleotide sequence encoding the variable region of the heavy chain	151
	Amino acid sequence encoding the variable region of the heavy chain	152
	Nucleotide sequence encoding the variable region of the lambda light chain	153
	Amino acid sequence encoding the variable region of the lambda light chain	154
	Nucleotide sequence encoding the variable region of the kappa light chain	155
	Amino acid sequence encoding the variable region of the kappa light chain	156
2.21	Nucleotide sequence encoding the variable region of the heavy chain	157
	Amino acid sequence encoding the variable region of the heavy chain	158
	Nucleotide sequence encoding the variable region of the light chain	159
	Amino acid sequence encoding the variable region of the light chain	160
3.1	Nucleotide sequence encoding the variable region of the heavy chain	161
	Amino acid sequence encoding the variable region of the heavy chain	162
	Nucleotide sequence encoding the variable region of the light chain	163
	Amino acid sequence encoding the variable region of the light chain	164
3.2	Nucleotide sequence encoding the variable region of the heavy chain	165
	Amino acid sequence encoding the variable region of the heavy chain	166
	Nucleotide sequence encoding the variable region of the light chain	167
	Amino acid sequence encoding the variable region of the light chain	168
3.4	Nucleotide sequence encoding the variable region of the heavy chain	169
	Amino acid sequence encoding the variable region of the heavy chain	170
	Nucleotide sequence encoding the variable region of the light chain	171
	Amino acid sequence encoding the variable region of the light chain	172
3.5	Nucleotide sequence encoding the variable region of the heavy chain	173
	Amino acid sequence encoding the variable region of the heavy chain	174
	Nucleotide sequence encoding the variable region of the light chain	175
	Amino acid sequence encoding the variable region of the light chain	176
3.6	Nucleotide sequence encoding the variable region of the heavy chain	177
	Amino acid sequence encoding the variable region of the heavy chain	178
	Nucleotide sequence encoding the variable region of the light chain	179
	Amino acid sequence encoding the variable region of the light chain	180
3.8	Nucleotide sequence encoding the variable region of the heavy chain	181
	Amino acid sequence encoding the variable region of the heavy chain	182

	Nucleotide sequence encoding the variable region of the light chain	183
	Amino acid sequence encoding the variable region of the light chain	184
3.9	Nucleotide sequence encoding the variable region of the heavy chain	185
	Amino acid sequence encoding the variable region of the heavy chain	186
	Nucleotide sequence encoding the variable region of the light chain	187
	Amino acid sequence encoding the variable region of the light chain	188
4.3	Nucleotide sequence encoding the variable region of the heavy chain	189
	Amino acid sequence encoding the variable region of the heavy chain	190
	Nucleotide sequence encoding the variable region of the light chain	191
	Amino acid sequence encoding the variable region of the light chain	192
4.4	Nucleotide sequence encoding the variable region of the heavy chain	193
	Amino acid sequence encoding the variable region of the heavy chain	194
	Nucleotide sequence encoding the variable region of the light chain	195
	Amino acid sequence encoding the variable region of the light chain	196
4.7	Nucleotide sequence encoding the variable region of the heavy chain	197
	Amino acid sequence encoding the variable region of the heavy chain	198
	Nucleotide sequence encoding the variable region of the light chain	199
	Amino acid sequence encoding the variable region of the light chain	200
4.8	Nucleotide sequence encoding the variable region of the heavy chain	201
	Amino acid sequence encoding the variable region of the heavy chain	202
	Nucleotide sequence encoding the variable region of the light chain	203
	Amino acid sequence encoding the variable region of the light chain	204
4.9	Nucleotide sequence encoding the variable region of the heavy chain	205
	Amino acid sequence encoding the variable region of the heavy chain	206
	Nucleotide sequence encoding the variable region of the light chain	207
	Amino acid sequence encoding the variable region of the light chain	208
4.10	Nucleotide sequence encoding the variable region of the heavy chain	209
	Amino acid sequence encoding the variable region of the heavy chain	210
	Nucleotide sequence encoding the variable region of the light chain	211
	Amino acid sequence encoding the variable region of the light chain	212
4.11	Nucleotide sequence encoding the variable region of the heavy chain	213
	Amino acid sequence encoding the variable region of the heavy chain	214
	Nucleotide sequence encoding the variable region of the light chain	215
	Amino acid sequence encoding the variable region of the light chain	216
4.12	Nucleotide sequence encoding the variable region of the heavy chain	217

	Amino acid sequence encoding the variable region of the heavy chain	218
	Nucleotide sequence encoding the variable region of the light chain	219
	Amino acid sequence encoding the variable region of the light chain	220
4.13	Nucleotide sequence encoding the variable region of the heavy chain	221
	Amino acid sequence encoding the variable region of the heavy chain	222
	Nucleotide sequence encoding the variable region of the light chain	223
	Amino acid sequence encoding the variable region of the light chain	224
4.14	Nucleotide sequence encoding the variable region of the heavy chain	225
	Amino acid sequence encoding the variable region of the heavy chain	226
	Nucleotide sequence encoding the variable region of the light chain	227
	Amino acid sequence encoding the variable region of the light chain	228
4.15	Nucleotide sequence encoding the variable region of the heavy chain	229
	Amino acid sequence encoding the variable region of the heavy chain	230
	Nucleotide sequence encoding the variable region of the light chain	231
	Amino acid sequence encoding the variable region of the light chain	232
4.16	Nucleotide sequence encoding the variable region of the heavy chain	233
	Amino acid sequence encoding the variable region of the heavy chain	234
	Nucleotide sequence encoding the variable region of the light chain	235
	Amino acid sequence encoding the variable region of the light chain	236
4.17	Nucleotide sequence encoding the variable region of the heavy chain	237
	Amino acid sequence encoding the variable region of the heavy chain	238
	Nucleotide sequence encoding the variable region of the light chain	239
	Amino acid sequence encoding the variable region of the light chain	240
4.18	Nucleotide sequence encoding the variable region of the heavy chain	241
	Amino acid sequence encoding the variable region of the heavy chain	242
	Nucleotide sequence encoding the variable region of the light chain	243
	Amino acid sequence encoding the variable region of the light chain	244
4.19	Nucleotide sequence encoding the variable region of the heavy chain	245
	Amino acid sequence encoding the variable region of the heavy chain	246
	Nucleotide sequence encoding the variable region of the light chain	247
	Amino acid sequence encoding the variable region of the light chain	248

4.20	Nucleotide sequence encoding the variable region of the heavy chain	249
	Amino acid sequence encoding the variable region of the heavy chain	250
	Nucleotide sequence encoding the variable region of the light chain	251
	Amino acid sequence encoding the variable region of the light chain	252
4.21	Nucleotide sequence encoding the variable region of the heavy chain	253
	Amino acid sequence encoding the variable region of the heavy chain	254
	Nucleotide sequence encoding the variable region of the light chain	255
	Amino acid sequence encoding the variable region of the light chain	256
4.22	Nucleotide sequence encoding the variable region of the heavy chain	257
	Amino acid sequence encoding the variable region of the heavy chain	258
	Nucleotide sequence encoding the variable region of the light chain	259
	Amino acid sequence encoding the variable region of the light chain	260
4.23	Nucleotide sequence encoding the variable region of the heavy chain	261
	Amino acid sequence encoding the variable region of the heavy chain	262
	Nucleotide sequence encoding the variable region of the light chain	263
	Amino acid sequence encoding the variable region of the light chain	264

Definitions

[0068] Unless otherwise defined, scientific and technical terms used herein shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. *See e.g.,* Sambrook et al. *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0069] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0070] The term "TNFa" refers to the cytokine, Tumor Necrosis Factor-alpha (Pennica, D. *et al.*, 1984, *Nature* 312:724-729). TNFa is also known in the art as cachectin.

[0071] The term "neutralizing" when referring to an antibody relates to an antibody's ability to eliminate or significantly reduce an effector function of a target antigen to which is binds. Accordingly, a "neutralizing" anti-TNFa antibody is capable of eliminating or significantly reducing an effector function, such as TNFa activity.

[0072] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0073] The term "isolated protein" referred to herein means a protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated protein" (1) is not associated with proteins found in nature, (2) is free of other proteins from the same source, e.g. free of murine proteins, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0074] The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein, fragments, and analogs are species of the polypeptide genus. Preferred polypeptides in accordance with the invention comprise the human heavy chain immunoglobulin molecules and the human kappa light chain immunoglobulin molecules, as well as antibody molecules formed by combinations comprising the heavy chain immunoglobulin molecules with light chain immunoglobulin molecules, such as the kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof.

[0075] The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring.

[0076] The term "operably linked" as used herein refers to positions of components so described that are in a relationship permitting them to function in their intended manner. For example, a control sequence "operably linked" to a coding sequence is connected in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

[0077] The term "control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are connected. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

[0078] The term "polynucleotide" as referred to herein means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[0079] The term "oligonucleotide" referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, e.g. for probes; although oligonucleotides may be double stranded, e.g. for use in the construction of a gene mutant. Oligonucleotides can be either sense or antisense oligonucleotides.

[0080] The term "naturally occurring nucleotides" referred to herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein includes oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. *See e.g.,* LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984); Stein et al. *Nucl. Acids Res.* 16:3209 (1988); Zon et al. *Anti-Cancer Drug Design* 6:539 (1991); Zon et al. *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Patent No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990). An oligonucleotide can include a label for detection, if desired.

[0081] The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic

acid sequence homology between the polynucleotides, oligonucleotides, or antibody fragments and a nucleic acid sequence of interest will be at least 80%, and more typically with preferably increasing homologies of at least 85%, 90%, 95%, 99%, and 100%.

[0082] Two amino acid sequences are "homologous" if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least about 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. *See* Dayhoff, M.O., in *Atlas of Protein Sequence and Structure*, pp. 101-110 (Volume 5, National Biomedical Research Foundation (1972)) and Supplement 2 to this volume, pp. 1-10. The two sequences or parts thereof are more preferably homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program.

[0083] The term "corresponds to" is used herein to mean that a polynucleotide sequence is homologous (i.e., is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence, or that a polypeptide sequence is identical to a reference polypeptide sequence.

[0084] In contradistinction, the term "complementary to" is used herein to mean that the complementary sequence is homologous to all or a portion of a reference polynucleotide sequence. For illustration, the nucleotide sequence "TATAC" corresponds to a reference sequence "TATAC" and is complementary to a reference sequence "GTATA".

[0085] The following terms are used to describe the sequence relationships between two or more polynucleotide or amino acid sequences: "reference sequence", "comparison window", "sequence identity", "percentage of sequence identity", and "substantial identity". A "reference sequence" is a defined sequence used as a basis for a sequence comparison. A reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA or gene sequence given in a sequence listing or may comprise a complete cDNA or gene sequence. Generally, a reference sequence is at least 18 nucleotides or 6 amino acids in length, frequently at least 24 nucleotides or 8 amino acids in length, and often at least 48 nucleotides or 16 amino acids in length. Since two polynucleotides or amino acid sequences may each (1) comprise a sequence (i.e., a portion of the complete polynucleotide or amino acid sequence) that is similar between the two molecules, and (2) may further comprise a sequence that is divergent between the two polynucleotides or amino acid sequences, sequence comparisons between two (or more) molecules are typically performed by comparing sequences of the two molecules over a "comparison window"

to identify and compare local regions of sequence similarity. A "comparison window", as used herein, refers to a conceptual segment of at least about 18 contiguous nucleotide positions or about 6 amino acids wherein the polynucleotide sequence or amino acid sequence is compared to a reference sequence of at least 18 contiguous nucleotides or 6 amino acid sequences and wherein the portion of the polynucleotide sequence in the comparison window may include additions, deletions, substitutions, and the like (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson and Lipman *Proc. Natl. Acad. Sci. (U.S.A.)* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, (Genetics Computer Group, 575 Science Dr., Madison, Wis.), GENEWORKS™, or MACVECTOR® software packages), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected.

[0086] The term "sequence identity" means that two polynucleotide or amino acid sequences are identical (i.e., on a nucleotide-by-nucleotide or residue-by-residue basis) over the comparison window. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the comparison window (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The terms "substantial identity" as used herein denotes a characteristic of a polynucleotide or amino acid sequence, wherein the polynucleotide or amino acid comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more preferably at least 99 percent sequence identity, as compared to a reference sequence over a comparison window of at least 18 nucleotide (6 amino acid) positions, frequently over a window of at least 24-48 nucleotide (8-16 amino acid) positions, wherein the percentage of sequence identity is calculated by comparing the reference sequence to the sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the comparison window. The reference sequence may be a subset of a larger sequence.

[0087] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See Immunology - A Synthesis* (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)). Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-

alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0088] Similarly, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences".

[0089] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity, and most preferably at least 99 percent sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamic-aspartic, and asparagine-glutamine.

[0090] As discussed herein, minor variations in the amino acid sequences of antibodies or immunoglobulin molecules are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75%, more preferably at least 80%, 90%, 95%, and most preferably 99% sequence identity to the antibodies or immunoglobulin molecules described herein. In particular, conservative amino acid replacements

are contemplated. Conservative replacements are those that take place within a family of amino acids that have related side chains. Genetically encoded amino acids are generally divided into families: (1) acidic=aspartate, glutamate; (2) basic=lysine, arginine, histidine; (3) non-polar=alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar=glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. More preferred families are: serine and threonine are an aliphatic-hydroxy family; asparagine and glutamine are an amide-containing family; alanine, valine, leucine and isoleucine are an aliphatic family; and phenylalanine, tryptophan, and tyrosine are an aromatic family. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding function or properties of the resulting molecule, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional peptide can readily be determined by assaying the specific activity of the polypeptide derivative. Assays are described in detail herein. Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie et al. *Science* 253:164 (1991). Thus, the foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the antibodies described herein.

[0091] Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H.

Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et at. *Nature* 354:105 (1991).

[0092] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence deduced, for example, from a full-length cDNA sequence. Fragments typically are at least 5, 6, 8 or 10 amino acids long, preferably at least 14 amino acids long, more preferably at least 20 amino acids long, usually at least 50 amino acids long, and even more preferably at least 70 amino acids long. The term "analog" as used herein refers to polypeptides which are comprised of a segment of at least 25 amino acids that has substantial identity to a portion of a deduced amino acid sequence and which has at least one of the following properties: (1) specific binding to a TNFa, under suitable binding conditions, (2) ability to block appropriate TNFa binding, or (3) ability to inhibit TNFa activity. Typically, polypeptide analogs comprise a conservative amino acid substitution (or addition or deletion) with respect to the naturally-occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally-occurring polypeptide.

[0093] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, *J. Adv. Drug Res.* 15:29 (1986); Veber and Freidinger *TINS* p.392 (1985); and Evans et al. *J. Med. Chem.* 30:1229 (1987). Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH_2NH--, --CH_2S--, --CH_2-CH_2--, --CH=CH--(cis and trans), --$COCH_2$--, --$CH(OH)CH_2$--, and --CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0094] "Antibody" or "antibody peptide(s)" refer to an intact antibody, or a binding fragment thereof, that competes with the intact antibody for specific binding. Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact

antibodies. Binding fragments include Fab, Fab', $F(ab')_2$, Fv, and single-chain antibodies. An antibody other than a "bispecific" or "bifunctional" antibody is understood to have each of its binding sites identical. An antibody substantially inhibits adhesion of a receptor to a counterreceptor when an excess of antibody reduces the quantity of receptor bound to counterreceptor by at least about 20%, 40%, 60% or 80%, and more usually greater than about 85% (as measured in an *in vitro* competitive binding assay).

[0095] The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is ≤ 1 μM, preferably ≤ 100 nM and most preferably ≤ 10 nM.

[0096] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0097] "Active" or "activity" in regard to a TNFa polypeptide refers to a portion of a TNFa polypeptide which has a biological or an immunological activity of a native TNFa polypeptide. "Biological" when used herein refers to a biological function that results from the activity of the native TNFa polypeptide. A preferred TNFa biological activity includes, for example, TNFa induced apoptosis.

[0098] "Mammal" when used herein refers to any animal that is considered a mammal. Preferably, the mammal is human.

[0099] Digestion of antibodies with the enzyme, papain, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no antigen-binding activity but having the ability to crystallize. Digestion of antibodies with the enzyme, pepsin, results in the a $F(ab')_2$ fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The $F(ab')_2$ fragment has the ability to crosslink antigen.

[0100] "Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites.

[0101] "Fab" when used herein refers to a fragment of an antibody which comprises the constant domain of the light chain and the CH1 domain of the heavy chain.

[0102] The term "mAb" refers to monoclonal antibody.

[0103] The description of XENOMAX® antibody sequences is coded as follows: "AB"-referring to antibody, "TNFa"-referring to antibody's binding specificity, "X" referring to XENOMOUSE® derived, "G1"-referring to IgG1 isotype or "G2" referring to IgG2 isotype, the last three digits referring to the single cell number from which the antibody was derived, for example: AB-TNFa-XG1-015.

[0104] The term "SC" refers to single cell and a particular XENOMAX® derived antibody may be referred to as SC followed by three digits, or just three digits, referring to the single cell number from which the antibody was derived herein.

[0105] The description of hybridoma derived antibody sequences is coded as follows: "AB"-referring to antibody, "TNFa"-refers to the antibody's binding specificity, "X" refers to XENOMOUSE® derived, "G1"-refers to IgG1 isotype or "G2" refers to IgG2 isotype, "K" refers to kappa, "L' refers to lambda. the last three digits referring to the clone from which the antibody was derived, for example: AB-TNFa-XG2K-4.17

[0106] "Liposome" when used herein refers to a small vesicle that may be useful for delivery of drugs that may include the TNFa polypeptide of the invention or antibodies to such a TNFa polypeptide to a mammal.

[0107] "Label" or "labeled" as used herein refers to the addition of a detectable moiety to a polypeptide, for example, a radiolabel, fluorescent label, enzymatic label chemiluminescent labeled or a biotinyl group. Radioisotopes or radionuclides may include ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, fluorescent labels may include rhodamine, lanthanide phosphors or FITC and enzymatic labels may include horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase.

[0108] The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient. Other chemistry terms herein are used according to conventional usage in the art, as exemplified by *The McGraw-Hill Dictionary of Chemical Terms* (Parker, S., Ed., McGraw-Hill, San Francisco (1985)).

[0109] As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition), and preferably a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present. Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, more preferably more than about 85%, 90%, 95%, and 99%. Most preferably, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[0110] The term "patient" includes human and veterinary subjects.

[0111] The term "SLAM®" refers to the "Selected Lymphocyte Antibody Method" (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996), and Schrader, US Patent No. 5,627,052).

[0112] The term "XENOMAX®" refers use of to the use of the "Selected Lymphocyte Antibody Method" (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996)), when used with XENOMOUSE® animals.

Antibody Structure

[0113] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. *See generally, Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair form the antibody binding site.

[0114] Thus, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

[0115] The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk *J. Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0116] A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.,* Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. *J. Immunol.* 148:1547-1553 (1992). Production of bispecific antibodies can be a relatively labor intensive process compared with production of conventional antibodies and yields and degree of purity are generally lower for bispecific antibodies. Bispecific antibodies do not exist in the form of fragments having a single binding site (e.g., Fab, Fab', and Fv).

Human Antibodies and Humanization of Antibodies

[0117] Human antibodies avoid some of the problems associated with antibodies that possess murine or rat variable and/or constant regions. The presence of such murine or rat derived proteins can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient. In order to avoid the utilization of murine or rat derived antibodies, fully human antibodies can be generated through the introduction of human antibody function into a rodent so that the rodent produces fully human antibodies.

[0118] One method for generating fully human antibodies is through the use of XENOMOUSE® strains of mice which have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. *See* Green et al. *Nature Genetics* 7:13-21 (1994). The XENOMOUSE® strains are available from Abgenix, Inc. (Fremont, CA).

[0119] The production of the XENOMOUSE® is further discussed and delineated in U.S. Patent Application Serial Nos. 07/466,008, filed January 12, 1990, 07/610,515, filed November 8, 1990, 07/919,297, filed July 24, 1992, 07/922,649, filed July 30, 1992, filed 08/031,801, filed March 15,1993, 08/112,848, filed August 27, 1993, 08/234,145, filed April 28, 1994, 08/376,279, filed January 20, 1995, 08/430, 938, April 27, 1995, 08/464,584, filed June 5, 1995, 08/464,582, filed June 5, 1995, 08/463,191, filed June 5, 1995, 08/462,837, filed June 5, 1995, 08/486,853, filed June 5, 1995, 08/486,857, filed June 5, 1995, 08/486,859, filed June 5, 1995, 08/462,513, filed June 5, 1995, 08/724,752, filed October 2, 1996, and 08/759,620, filed December 3, 1996 and U.S. Patent Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). *See also* European Patent No., EP 0 463 151 B1, grant published June 12, 1996, International Patent Application No., WO 94/02602, published February 3, 1994, International Patent Application No., WO 96/34096, published October 31, 1996, WO 98/24893, published June 11, 1998, WO 00/76310, published December 21, 2000. The disclosures of each of the above-cited patents, applications.

[0120] In an alternative approach, others, including GenPharm International, Inc., have utilized a "minilocus" approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Patent No. 5,545,807 to Surani et al. and U.S. Patent Nos. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,877,397, 5,874,299, and 6,255,458 each to Lonberg and Kay, U.S. Patent No. 5,591,669 and 6,023.010 to

Krimpenfort and Berns, U.S. Patent Nos. 5,612,205, 5,721,367, and 5,789,215 to Berns et al., and U.S. Patent No. 5,643,763 to Choi and Dunn, and GenPharm International U.S. Patent Application Serial Nos. 07/574,748, filed August 29, 1990, 07/575,962, filed August 31, 1990, 07/810,279, filed December 17, 1991, 07/853,408, filed March 18, 1992, 07/904,068, filed June 23, 1992, 07/990,860, filed December 16, 1992, 08/053,131, filed April 26, 1993, 08/096,762, filed July 22, 1993, 08/155,301, filed November 18, 1993, 08/161,739, filed December 3, 1993, 08/165,699, filed December 10, 1993, 08/209,741, filed March 9, 1994. *See also* European Patent No. 0 546 073 B1, International Patent Application Nos. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Patent No. 5,981,175. *See further* Taylor et al., 1992, Chen et al., 1993, Tuaillon et al., 1993, Choi et al., 1993, Lonberg et al., (1994), Taylor et al., (1994), and Tuaillon et al., (1995), Fishwild et al., (1996).

[0121] Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. *See* European Patent Application Nos. 773 288 and 843 961.

[0122] Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies have a human constant region and a murine variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide fully human antibodies against TNFa in order to vitiate concerns and/or effects of HAMA or HACA response.

Antibody Therapeutics

[0123] As discussed herein, the function of the TNFa antibody appears important to at least a portion of its mode of operation. By function, is meant, by way of example, the activity of the TNFa antibody in operation with TNFa. Accordingly, in certain respects, it may be desirable in connection with the generation of antibodies as therapeutic candidates against TNFa that the antibodies be capable of fixing complement and participating in CDC. There are a number of isotypes of antibodies that are capable of the same, including, without limitation, the following: murine IgM, murine IgG2a, murine IgG2b, murine IgG3, human IgM, human IgG1, and human IgG3. It will be appreciated that antibodies that are generated need not initially possess such an isotype but, rather, the antibody as generated can possess any isotype and the antibody can be isotype switched thereafter using conventional techniques that are well known in the art. Such techniques include the use of direct recombinant techniques (*see e.g.*, U.S. Patent No. 4,816,397), cell-cell fusion techniques (*see e.g.*, U.S. Patent Nos. 5,916,771 and 6,207,418), among others.

[0124] In the cell-cell fusion technique, a myeloma or other cell line is prepared that possesses a heavy chain with any desired isotype and another myeloma or other cell line is prepared

that possesses the light chain. Such cells can, thereafter, be fused and a cell line expressing an intact antibody can be isolated.

[0125] By way of example, the TNFa antibody discussed herein is a human anti-TNFa IgG2 antibody. If such antibody possessed desired binding to the TNFa molecule, it could be readily isotype switched to generate a human IgM, human IgG1, or human IgG3 isotype, while still possessing the same variable region (which defines the antibody's specificity and some of its affinity). Such molecule would then be capable of fixing complement and participating in CDC.

[0126] Accordingly, as antibody candidates are generated that meet desired "structural" attributes as discussed above, they can generally be provided with at least certain of the desired "functional" attributes through isotype switching.

Design and Generation of Other Therapeutics

[0127] In accordance with the present invention and based on the activity of the antibodies that are produced and characterized herein with respect to TNFa, the design of other therapeutic modalities beyond antibody moieties is facilitated. Such modalities include, without limitation, advanced antibody therapeutics, such as bispecific antibodies, immunotoxins, and radiolabeled therapeutics, generation of peptide therapeutics, gene therapies, particularly intrabodies, antisense therapeutics, and small molecules.

[0128] In connection with the generation of advanced antibody therapeutics, where complement fixation is a desirable attribute, it may be possible to sidestep the dependence on complement for cell killing through the use of bispecifics, immunotoxins, or radiolabels, for example.

[0129] For example, in connection with bispecific antibodies, bispecific antibodies can be generated that comprise (i) two antibodies one with a specificity to TNFa and another to a second molecule that are conjugated together, (ii) a single antibody that has one chain specific to TNFa and a second chain specific to a second molecule, or (iii) a single chain antibody that has specificity to TNFa and the other molecule. Such bispecific antibodies can be generated using techniques that are well known; for example, in connection with (i) and (ii) *see e.g.,* Fanger et al. *Immunol Methods* 4:72-81 (1994) and Wright and Harris, *supra.* and in connection with (iii) *see e.g.,* Traunecker et al. *Int. J. Cancer (Suppl.)* 7:51-52 (1992). In each case, the second specificity can be made to the heavy chain activation receptors, including, without limitation, CD16 or CD64 (*see e.g.,* Deo et al. 18:127 (1997)) or CD89 (*see e.g.,* Valerius et al. *Blood* 90:4485-4492 (1997)). Bispecific antibodies prepared in accordance with the foregoing would be likely to kill cells expressing TNFa.

[0130] In connection with immunotoxins, antibodies can be modified to act as immunotoxins utilizing techniques that are well known in the art. *See e.g.,* Vitetta *Immunol Today* 14:252 (1993). *See also* U.S. Patent No. 5,194,594. In connection with the preparation of

radiolabeled antibodies, such modified antibodies can also be readily prepared utilizing techniques that are well known in the art. *See e.g.,* Junghans et al. in *Cancer Chemotherapy and Biotherapy* 655-686 (2d edition, Chafner and Longo, eds., Lippincott Raven (1996)). *See also* U.S. Patent Nos. 4,681,581, 4,735,210, 5,101,827, 5,102,990 (RE 35,500), 5,648,471, and 5,697,902. Each of immunotoxins and radiolabeled molecules would be likely to kill cells expressing TNFa.

Preparation of Antibodies

[0131] Antibodies, as described herein, were prepared through the utilization of the XENOMOUSE® technology, as described below. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed in the background section herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996 and International Patent Application Nos. WO 98/24893, published June 11, 1998 and WO 00/76310, published December 21, 2000. *See also* Mendez et al. *Nature Genetics* **15**:146-156 (1997).

[0132] Through use of such technology, fully human monoclonal antibodies to a variety of antigens have been produced. Essentially, XENOMOUSE® lines of mice are immunized with an antigen of interest (e.g. TNFa), lymphatic cells (such as B-cells) are recovered from the mice that expressed antibodies, and the recovered cell lines are fused with a myeloid-type cell line to prepare immortal hybridoma cell lines. These hybridoma cell lines are screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. Provided herein are methods for the production of multiple hybridoma cell lines that produce antibodies specific to TNFa. Further, provided herein are characterization of the antibodies produced by such cell lines, including nucleotide and amino acid sequence analyses of the heavy and light chains of such antibodies.

[0133] Alternatively, instead of being fused to myeloma cells to generate hybridomas, the recovered cells, isolated from immunized XENOMOUSE® lines of mice, are screened further for reactivity against the initial antigen, preferably TNFa protein. Such screening includes ELISA with TNFa protein, a competition assay with known antibodies that bind the antigen of interest, *in vitro* neutralization of TNFa induced apoptosis and *in vitro* binding to transiently transfected CHO cells expressing full length TNFa. Single B cells secreting antibodies of interest are then isolated using a TNFa-specific hemolytic plaque assay (Babcook et al., *Proc. Natl. Acad. Sci. USA,* i93:7843-7848 (1996)). Cells targeted for lysis are preferably sheep red blood cells (SRBCs) coated with the TNFa antigen. In the presence of a B cell culture secreting the immunoglobulin of

interest and complement, the formation of a plaque indicates specific TNFa-mediated lysis of the target cells. The single antigen-specific plasma cell in the center of the plaque can be isolated and the genetic information that encodes the specificity of the antibody is isolated from the single plasma cell. Using reverse-transcriptase PCR, the DNA encoding the variable region of the antibody secreted can be cloned. Such cloned DNA can then be further inserted into a suitable expression vector, preferably a vector cassette such as a pcDNA, more preferably such a pcDNA vector containing the constant domains of immunoglobulin heavy and light chain. The generated vector can then be transfected into host cells, preferably CHO cells, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. Herein, is described the isolation of multiple single plasma cells that produce antibodies specific to TNFa. Further, the genetic material that encodes the specificity of the anti-TNFa antibody is isolated, and introduced into a suitable expression vector which is then transfected into host cells.

[0134] In general, antibodies produced by the above-mentioned cell lines possessed fully human IgG1 or IgG2 heavy chains with human kappa light chains. The antibodies possessed high affinities, typically possessing Kd's of from about 10^{-9} through about 10^{-13} M, when measured by either solid phase and solution phase.

[0135] As will be appreciated, anti-TNFa antibodies can be expressed in cell lines other than hybridoma cell lines. Sequences encoding particular antibodies can be used for transformation of a suitable mammalian host cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. The transformation procedure used depends upon the host to be transformed. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0136] Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. Cell lines of particular preference are selected through determining which cell lines have high expression levels and produce antibodies with constitutive TNFa binding properties.

[0137] Anti-TNFa antibodies are useful in the detection of TNFa in patient samples and accordingly are useful as diagnostics for disease states as described herein. In addition, based

on their ability to significantly neutralize TNFa activity (as demonstrated in the Examples below), anti-TNFa antibodies will have therapeutic effects in treating symptoms and conditions resulting from TNFa. In specific embodiments, the antibodies and methods herein relate to the treatment of symptoms resulting from TNFa including: fever, muscle ache, lethargy, headache, nausea, and inflammation. Further embodiments involve using the antibodies and methods described herein to treat: cachexia, anorexia, rheumatic diseases such as arthritis, inflammatory diseases such as Crohn's disease, and auto-immune diseases, such as psoriasis, graft-host reactions, and septic shock.

Therapeutic Administration and Formulations

[0138] Biologically active anti-TNFa antibodies as described herein may be used in a sterile pharmaceutical preparation or formulation to reduce the level of serum TNFa thereby effectively treating pathological conditions where, for example, serum TNFa is abnormally elevated. Anti-TNFa antibodies preferably possess adequate affinity to potently suppress TNFa to within the target therapeutic range, and preferably have an adequate duration of action to allow for infrequent dosing. A prolonged duration of action will allow for less frequent and more convenient dosing schedules by alternate parenteral routes such as subcutaneous or intramuscular injection.

[0139] When used for *in vivo* administration, the antibody formulation must be sterile. This is readily accomplished, for example, by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. The antibody ordinarily will be stored in lyophilized form or in solution. Therapeutic antibody compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having an adapter that allows retrieval of the formulation, such as a stopper pierceable by a hypodermic injection needle.

[0140] The route of antibody administration is in accord with known methods, e.g., injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intrathecal, inhalation or intralesional routes, or by sustained release systems as noted below. The antibody is preferably administered continuously by infusion or by bolus injection.

[0141] An effective amount of antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it is preferred that the therapist titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. Typically, the clinician will administer antibody until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays or by the assays described herein.

[0142] Antibodies, as described herein, can be prepared in a mixture with a pharmaceutically acceptable carrier. This therapeutic composition can be administered intravenously or through the nose or lung, preferably as a liquid or powder aerosol (lyophilized).

The composition may also be administered parenterally or subcutaneously as desired. When administered systemically, the therapeutic composition should be sterile, pyrogen-free and in a parenterally acceptable solution having due regard for pH, isotonicity, and stability. These conditions are known to those skilled in the art. Briefly, dosage formulations of the compounds described herein are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients, or stabilizers. Such materials are non-toxic to the recipients at the dosages and concentrations employed, and include buffers such as TRIS HCl, phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium and/or nonionic surfactants such as TWEEN, PLURONICS or polyethyleneglycol.

[0143] Sterile compositions for injection can be formulated according to conventional pharmaceutical practice as described in *Remington: The Science and Practice of Pharmacy* (20th ed, Lippincott Williams & Wilkens Publishers (2003)). For example, dissolution or suspension of the active compound in a vehicle such as water or naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

[0144] Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the polypeptide, which matrices are in the form of shaped articles, films or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (e.g., poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, *J. Biomed Mater. Res.*, (1981) 15:167-277 and Langer, *Chem. Tech.*, (1982) 12:98-105, or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers*, (1983) 22:547-556), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the LUPRON Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

[0145] While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated proteins remain in the body for a long time, they may denature or

aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for protein stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0146] Sustained-released compositions also include preparations of crystals of the antibody suspended in suitable formulations capable of maintaining crystals in suspension . These preparations when injected subcutaneously or intraperitonealy can produce a sustain release effect. Other compositions also include liposomally entrapped antibodies. Liposomes containing such antibodies are prepared by methods known per se: U.S. Pat. No. DE 3,218,121; Epstein *et al., Proc. Natl. Acad. Sci. USA*, (1985) 82:3688-3692; Hwang *et al., Proc. Natl. Acad. Sci. USA*, (1980) 77:4030-4034; EP 52,322; EP 36,676; EP 88,046; EP 143,949; 142,641; Japanese patent application 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324.

[0147] The dosage of the antibody formulation for a given patient will be determined by the attending physician taking into consideration various factors known to modify the action of drugs including severity and type of disease, body weight, sex, diet, time and route of administration, other medications and other relevant clinical factors. Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods.

[0148] An effective amount of the antibodies, described herein, to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it is preferred for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. A typical daily dosage might range from about 0.001mg/kg to up to 100mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer the therapeutic antibody until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays or as described herein.

[0149] It will be appreciated that administration of therapeutic entities in accordance with the compositions and methods herein will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible

and tolerable with the route of administration. *See also* Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." *Regul. Toxicol. Pharmacol.* 32(2):210-8 (2000), Wang W. "Lyophilization and development of solid protein pharmaceuticals." *Int. J. Pharm.* 203(1-2):1-60 (2000), Charman WN "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." *J Pharm Sci* .89(8):967-78 (2000), Powell et al. "Compendium of excipients for parenteral formulations" *PDA J Pharm Sci Technol.* 52:238-311 (1998) and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

[0150] It is expected that the antibodies described herein will have therapeutic effect in treatment of symptoms and conditions resulting from TNFa. In specific embodiments, the antibodies and methods herein relate to the treatment of symptoms resulting from TNFa including: fever, muscle ache, lethargy, headache, nausea, and inflammation. Further embodiments, involve using the antibodies and methods described herein to treat: cachexia, anorexia, rheumatic diseases such as arthritis, inflammatory diseases such as Crohn's disease, auto-immune diseases, such as psoriasis, graft-host reactions, and septic shock.

EXAMPLES

[0151] The following examples, including the experiments conducted and results achieved are provided for illustrative purposes only and are not to be construed as limiting upon the teachings herein.

EXAMPLE 1

ANTIGEN PREPARATION

TNFa-KLH Antigen Preparation for Immunization of XENOMOUSE® animals

[0152] Recombinant human TNFa was obtained from R&D Systems (Minneapolis, MN Cat. No. 210-TA/CF). The TNFa-KLH antigen, used for the immunization of XENOMOUSE® animals, was prepared as follows: human TNF-α (200 μg) (R&D) was mixed with 50 μg of keyhole limpet hemocyanin (KLH; Pierce, Rockford, IL) to a final volume of 165 μl using distilled water. 250 μl of conjugation buffer (0.1M MES, 0.9M NaCl, pH 4.7) was added and TNFa and KLH were crosslinked by the addition of 25 μl of 10mg/mL stock solution of 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC, Pierce, Rockford, IL). The conjugate was incubated for 2 hours at room temperature and the unreacted EDC was removed by centrifugation through a 1 kDa filter (Centrifugal filter; Millipore, Bedford, MA) using PBS pH 7.4.

TNFa-TCE Antigen Preparation for Immunization of XENOMOUSE® animals

[0153] Human TNFa was recombinantly generated as a fusion protein in frame with a universal T-cell epitope (TCE) (J. Immunol 1992 148(5):1499) for immunization of XENOMOUSE® animals.

[0154] Human TNFa was cloned from human peripheral mononuclear cells (PBMCs). mRNA was isolated from purified hPBMC's and cDNA was generated by reverse transcription. Human TNFa was specifically amplified by PCR and cloned in frame with a universal T-cell epitope (TCE) derived from Tetanus toxin in the expression vector pGEX (Amersham Pharmacia). The fusion protein was expressed in *E. Coli*, purified on Glutathione Sepharose beads (CAT# 17-0756-01, Amersham Pharmacia), cleaved with thrombin (Sigma) and eluted as described by the manufacturer (Amersham Pharmacia).

EXAMPLE 2

ANTIBODY GENERATION

Immunization

[0155] Human monoclonal antibodies against human TNFa were developed by sequentially immunizing XENOMOUSE® mice (XENOMOUSE® XMG2L3 or 3B-3L3 Abgenix, Inc. Fremont, CA).

[0156] To generate hybridomas, cohorts of XMG2L3 and 3B-L3 XENOMOUSE® mice were immunized with TNFa alone or TNFa with CPG via foot pad. The initial immunization was with 10 μg of antigen mixed 1:1 v/v with TITERMAX GOLD® (Sigma, Oakville, ON) per mouse. A subsequent four boosts were performed with 10μg of antigen mixed with alum (Sigma, Oakville, ON), adsorbed overnight, per mouse, followed by one injection with TNFa in TITERMAX GOLD®, one injection with alum and then a final boost of 10μg of TNFa in PBS per mouse.

[0157] Cohorts receiving TNFa with CPG were first immunized with TNFa and TITERMAX GOLD® as above, the next six boosts were with TNFa absorbed to Alum as previously stated along with CPG. The final boost was with TNFa in PBS and CPG. In particular, animals were immunized on days 0, 3, 9,16, 21, 25, 30 and 35. The animals were bled on days 28 and 39 to obtain sera for harvest selection as described below.

[0158] To generate mAbs by XENOMAX®, cohorts of XMG2 XENOMOUSE® mice were immunized with TNFa via foot pad (FP), TNFa-KLH (as prepared in Example 1) via base of the tail by subcutaneous injection and intraperitoneum (BIP), or with TNFa-TCE (as prepared in Example 1) via base of the tail by subcutaneous injection and intraperitoneum. For TNFa footpad immunizations, the initial immunization was with 2μg of antigen mixed 1:1 v/v with TITERMAX GOLD® per mouse. A subsequent four boosts were performed with 2 μg of antigen mixed with alum (Sigma, Oakville, ON), adsorbed overnight, per mouse, followed by one injection with TNFa

in TITERMAX GOLD®, one injection with alum and then a final boost of 2μg of TNFa in PBS per mouse. In particular, animals were immunized on days 0, 3, 7,10, 14, 17, 21 and 24. The animals were bled on day 19 to obtain sera for harvest selection as described below.

[0159] The initial BIP immunization with 2 or 5μg TNFa-KLH or TNFa-TCE respectively was mixed 1:1 v/v with Complete Freund's Adjuvant (CFA, Sigma, Oakville, ON) per mouse. Subsequent boosts were made first with 2 or 5μg of antigen respectively, mixed 1:1 v/v with Incomplete Freund's Adjuvant (IFA, Sigma, Oakville, ON) per mouse, followed by a final boost in PBS per mouse. The animals were immunized on days 0, 14, 28, 42, 56, and day 75 or 93 (final boost). The animals were bled on day 63 to obtain sera for harvest selection as described below.

[0160] To generate rabbit anti-hTNFa monoclonal antibodies by SLAM, a cohort of New Zealand white rabbits were immunized as follows. A primary boost consisting of 250 μg of TNFa-TCE, emulsified 1;1 v/v with complete freund's adjuvant (CFA), was given subcutaneously in four sites along the rabbit's dorsal body. These were followed by 3 immunizations with 125 μg of TNFa-TCE emulsified 1:1 v/v with incomplete freunds adjuvant (IFA) intramuscularly via the hind legs. Each of the boosts were separated by 21 days. The animals were bled prior to the fourth immunization for serology, see Table 9 below.

Selection of animals for harvest

[0161] Anti-hTNFa antibody titers were determined by ELISA. hTNFa was coated onto Costar Labcoat Universal Binding Polystyrene 96-well plates (Corning, Acton, MA) overnight at four degrees. The solution containing unbound TNFa was removed and the plates were treated with UV light (365nm) for 4 minutes (4000 microjoules). The plates were washed five times with dH_2O. XENOMOUSE® sera from the TNFa immunized animals, or naïve XENOMOUSE® animals, were titrated in 2% milk/PBS at 1:2 dilutions in duplicate from a 1:100 initial dilution. The last well was left blank. The plates were washed five times with dH_2O. A goat anti-human IgG Fc-specific horseradish peroxidase (HRP, Pierce, Rockford, IL) conjugated antibody was added at a final concentration of 1μg/mL for 1 hour at room temperature. The plates were washed five times with dH_2O. The plates were developed with the addition of TMB chromogenic substrate (Gaithersburg, MD) for 30 minutes and the ELISA was stopped by the addition of 1 M phosphoric acid. The specific titer of individual XENOMOUSE® animals was determined from the optical density at 450 nm and are shown in Tables 2 to 8 The titer represents the reciprocal dilution of the serum and therefore the higher the number the greater the humoral immune response to hTNFa.

[0162] Rabbit anti-TNFa titers were determined as above, but for detection of primary antibody, a goat anti-rabbit IgG heavy and light chain-specific horseradish peroxidase (HRP, Pierce, Rockford, IL) reagent was used in place of the anti-human reagent, see Table 9.

Table 2

FP, 3B-3L3 mice, hTNFa
G1 kλ

Mouse ID	Titer	
	day 28	day 39
N472-3	400	-
N473-11	310	-
N474-3	1,100	-
N543-3	8,000	6,500
N574-5	16,000	16,000
N638-7	-	-
N638-8	40	50

[0163] All XENOMOUSE® animals in Table 2 were selected for harvest and generation of hybridomas.

Table 3

FP, 3B-3L3 mice, hTNFa+CpG
G1 kλ

Mouse ID	Titer	
	day 28	day 39
N643-8	19,000	70,000
N651-9	24,000	75,000
N673-7	19,000	60,000
N713-7	750	6,000
N732-6	80	450

[0164] All XENOMOUSE® animals in Table 3 were selected for harvest and generation of hybridomas.

Table 4

FP, XMG2L3 mice, hTNFa

G2 kλ

Mouse ID	Titer	
	day 28	day 39
N668-1	50,000	-
N668-2	40,000	-
N668-3	22,000	-
N668-7	150,000	175,000
N670-1	22,000	24,000
N676-6	55,000	73,000
N677-3	110,000	150,000

[0165] All XENOMOUSE® animals in Table 4 were selected for harvest and generation of hybridomas.

Table 5

FP,XMG2L3mice, hTNFa+CpG

G2 kλ

Mouse ID	Titer	
	day 28	day 39
N667-1	175,000	600,000
N667-3	200,000	500,000
N667-5	400,000	200,000
N677-2	325,000	600,000
N677-4	21,000	300,000
N677-5	300,000	600,000

[0166] All XENOMOUSE® animals in Table 5 were selected for harvest and generation of hybridomas.

Table 6

FP, XMG2 mice, hTNFa

IgG2/K

Mouse ID	Titer
	Day 17
0651-1	186
0651-2	816
0651-3	388
0651-4	260

0651-5	1342
0651-6	373
0651-7	314
0651-8	<100 @ OD 0.666
0651-9	588
0651-10	163

[0167] XENOMOUSE® animals (0651-2, 0651-3, 0651-5 and 0651-9) were selected for XENOMAX® harvests based on the serology data in Table 6.

Table 7

BIP, XMG2 mice, hTNFa-KLH
IgG2/K

Mouse ID	**Titer**
	Day 63
O797-1	1999
O797-2	2586
O797-3	1885
O797-4	>6400 @ OD 2.074
O797-5	1492
O797-6	4325
O797-7	>6400 @ OD 3.294
O797-8	1314
O797-9	3329
O797-10	4829

[0168] XENOMOUSE® animals (O797-4, O797-6, O797-7 and O797-10) were selected for XENOMAX® harvests based on the serology data in Table 7.

Table 8

BIP, XMG2 mice, hTNFa-TCE
IgG2/K

Mouse ID	**Titer**
	Day 63
O796-1	2677
O796-2	5197
O796-3	3143
O796-4	>6400 @ OD 2.034

O796-5	1055
O796-6	221
O796-7	>6400 @ OD 2.017
O796-8	>6400 @ OD 2.066
O796-9	2145
O796-10	4364

[0169] XENOMOUSE® animals (O796-2, O796-4, O796-7, O796-8 and O796-10) were selected for XENOMAX® harvests based on the serology data in Table 8.

Table 9

Rabbit IPI-5	
Rabbit ID	**Titer**
	Day 63
IPI-5	500,000

[0170] Blood from rabbit IPI-5 was harvested for generating rabbit monoclonal antibodies by SLAM.

EXAMPLE 3

GENERATION OF ANTI-HUMAN TNFα ANTIBODIES

Generation of Anti-hTNFα Antibodies by Hybridoma.

Recovery of lymphocytes, B-cell isolations, fusions and generation of hybridomas

[0171] Immunized mice were sacrificed by cervical dislocation, and the lymph nodes harvested and pooled from each cohort. The lymphoid cells were dissociated by grinding in DMEM to release the cells from the tissues and the cells were suspended in DMEM. The cells were counted, and 0.9 mL DMEM per 100 million lymphocytes added to the cell pellet to resuspend the cells gently but completely. Using 100μL of $CD90^+$ magnetic beads per 100 million cells, the cells were labeled by incubating the cells with the magnetic beads at 4°C for 15 minutes. The magnetically labeled cell suspension containing up to 10^8 positive cells (or up to $2x10^9$ total cells) was loaded onto a LS^+ column and the column washed with DMEM. The total effluent was collected as the CD90-negative fraction (most of these cells are B cells).

[0172] P3 myeloma cells and B cell-enriched lymph node cells were combined in a ratio of 1:1 (myeloma:lymph nodes) into a 50 mL conical tube in DMEM. The combined cells were centrifuged at 800xg (2000 rpm) for 5-7 min. and the supernatant immediately removed from the resulting pellet. Two to four mL of Pronase solution (CalBiochem, Cat. #53702; 0.5mg/mL in PBS) was added to the cells to resuspend the cell pellet gently. The enzyme treatment was allowed

to proceed for no more than two minutes and the reaction stopped by the addition of 3-5 mL of FBS. Enough ECF solution was added to bring the total volume to 40 mL and the mixture was centrifuged at 800xg (2000 rpm) for 5-7 min. The supernatant was removed and the cell pellet gently resuspended with a small volume of ECF solution, followed by enough ECF solution to make a total volume of 40 mL. The cells were mixed well and counted, then centrifuged at 800xg (2000 rpm) for 5-7 min. The supernatant was removed and the cells resuspended in a small volume of ECF solution. Enough additional ECF solution was added to adjust the concentration to 2 x 10^6 cells/mL.

[0173] The cells were then placed in an Electro-Cell-Fusion (ECF) generator (Model ECM2001, Genetronic, Inc., San Diego, CA) and fused according to the manufacturer's instructions. After ECF, the cell suspensions were carefully removed from the fusion chamber under sterile conditions and transferred into a sterile tube containing the same volume of Hybridoma Medium in DMEM. The cells were incubated for 15-30 minutes at 37°C, then centrifuged at 400xg (1000 rpm) for five minutes. The cells were gently resuspended in a small volume of ½ HA medium (1 bottle of 50X HA from Sigma, Cat. #A9666 and 1 liter of Hybridoma Medium) and the volume adjusted appropriately with more ½ HA medium (based on 5x10^6 B cells per 96-well plate and 200µL per well). The cells were mixed well and pipetted into 96-well plates and allowed to grow. On day 7 or 10, one-half the medium was removed, and the cells re-fed with ½ HA medium.

Selection of candidate antibodies by ELISA

[0174] After 14 days of culture, hybridoma supernatants were screened for TNFa-specific monoclonal antibodies. The ELISA plates (Fisher, Cat. No. 12-565-136) were coated with 50µL/well of TNFa (2µg/mL) in Coating Buffer (0.1 M Carbonate Buffer, pH 9.6, $NaHCO_3$ 8.4 g/L), then incubated at 4°C overnight. After incubation, the plates were washed with Washing Buffer (0.05% Tween 20 in PBS) 3 times. 200µL/well Blocking Buffer (0.5% BSA, 0.1% Tween 20, 0.01% Thimerosal in 1x PBS) were added and the plates incubated at room temperature for 1 hour. After incubation, the plates were washed with Washing Buffer three times. 50µL/well of hybridoma supernatants, and positive and negative controls were added and the plates incubated at room temperature for 2 hours.

[0175] After incubation, the plates were washed three times with Washing Buffer. 100µL/well of goat anti-huIgGfc-HRP detection antibody (Caltag, Cat. #H10507), goat anti-hIg kappa-HRP (Southern Biotechnology, Cat. # 2060-05) and goat anti-hIg lambda (Southern Biotechnology, Cat. # 2070-05) were added and the plates were incubated at room temperature for 1 hour. After the incubation, the plates were washed three times with Washing Buffer. 100 ul/well of TMB (BioFX Lab. Cat. #TMSK-0100-01) were added and the plates allowed to develop for

about 10 minutes (until negative control wells barely started to show color), then 50 ul/well stop solution (TMB Stop Solution (BioFX Lab. Cat. #STPR-0100-01) were added and the plates read on an ELISA plate reader at wavelength 450nm. The number of positive wells is presented in Table 10.

Table 10

Group #	hIgG/hkappa	hIgG/hlamda	Total # positive
fusion 1+2 (3B-3L3)	9	9	18
fusion 3+4 (xgm2L3)	21	12	33

Secondary screen to determine the isotype and light chain usage for the anti-TNFa hybridoma supernatants using Luminex

[0176] The Luminex platform is a fluorescence bead based technology which enables one to run multiple assays at once. The Luminex reader is able to ascertain positive signaling events on different coded microspheres. This allows one to coat each bead separately, then mix the differentially coated microspheres together and then in one step assay antibody binding to each of the different microspheres. For isotyping antibodies, microspheres were coated in such a manner in that each bead was able to specifically bind a particular heavy chain or light chain isotype. The microspheres were then mixed together and hybridoma supernatant for each antibody was added. After a 20 minute incubation, the microspheres were washed, and the bound antibody was detected using a fluorescently labeled secondary antibody. The microspheres were then read using the Luminex reader. Table 10 shows number of each isotype found for the different fusion groups.

Neutralization of TNFa induced apoptosis assays by hybridoma anti-TNFa antibodies

[0177] 47 anti-TNFa hybridoma antibodies were assayed for their ability to neutralize the biological effect of TNFa induced apoptosis on human WM 266.4 cells. IgG was first enriched from each hybridoma supernatant by purification on Swell-Gel protein A (Pierce), and then eluted, neutralized, and quantified. 20,000 WM266.6 cells were plated in 96-well plates in complete media (RPMI1640/10%FBS/Gln/P/S) and incubated at 37°C/10%CO_2 overnight. Media was removed and 50μL of test antibodies and TNFa (pre-incubated for 30' at room temperature) were added in serum free media (RPMI1640/Gln/P/S). 50μL cyclohexamide plates were incubated overnight as above under the following final assay conditions: V=100 μl, cyclohexamide = 6μg/mL, TNFa = 600 pg/mL = 11.4 pM as a trimer, test antibodies concentrations vary as described. 100μL Caspase buffer and 0.3μL Caspase substrate (APO-ONE, Promega) were added to each well.

[0178] Caspase activity was determined on a Victor Wallac plate reader with the excitation wavelength @ 485 nm and the emission wavelength @ 530 nm. An example of the

neutralization of apoptosis by hybridoma derived antibodies is provided in Figure 1. Figure 1 shows a bar graph illustrating the effect that various TNFa antibodies had on neutralizing apoptosis in human WM 266.4 cells. A control (pos) shows the induction of apoptosis by TNFa in the presence of cyclohexamide alone. Another control shows inhibition of apoptosis by 6 nM mouse anti-hTNFa antibody (R&D). The Y-axis represents the relative amount of caspase 3/7 activity as an indication of TNFa induced apoptosis. As Figure 1 illustrates, antibodies, including 3.2, 3.7 and 4.17 were very potent at neutralizing TNFa induced apoptosis at 3 nM.

Neutralization of apoptosis by propidium iodide incorporation assay

[0179] The 47 anti-hTNFa hybridoma antibody supernatants were further assayed for their ability to neutralize the biological effect of TNFa induced apoptosis on human MCF-7 cells. 96-well plates were seeded at 5000 cells/well, 200µl/well with phenol red free DMEM + 10% FCS. The cells were incubated overnight at 37°C + 5% CO_2. On each plate a titration of hybridoma antibody (quantitated by capture ELISA, as described in Example 2, and compared to a standard curve control Ab) was assayed along-side Rabbit 014 control Ab from 10µg/mL to a final concentration of 0.005ng/mL (titrated 1:5) in apoptosis medium (2.5% FCS, 5µg/mL CHX in phenol red free DMEM), in triplicate, at a constant concentration of 100 pg/mL (1.9 pM as a trimer) TNFa. Six well plates with TNFa alone and 6 wells with apoptosis medium alone were also included. TNFa +/- neutralizing antibody was pre-incubated for 1 hour at 37°C + 5% CO_2. 200µL of antibody was then transferred to the cells and incubated overnight at 37°C + 5% CO_2.

[0180] Cells were stained with 0.5µg/mL PI and 2.5µg/mL Heochst 33342 for one hour. The percentage of apoptosis was determined by counting the number of dead cells (PI +ve) and dividing by the total number of cells (Heochst +ve). The ability of hybridoma derived, human anti-TNFa binding antibodies to neutralize TNFa induced apoptosis of MCF-7 cells was measured by propidium iodide uptake as a ratio of the number of total cells by Heochst 33342 staining. SLAM derived rabbit mAb, R014, as well as various other human mAbs, including 3.2, 4.17 and 3.7 were very potent at neutralizing TNFa induced apoptosis of MCF-7 cells.

Isoptype switching and expression of IgG2 hybridomas 4.17 and 3.2

[0181] mRNA was extracted from hybridomas 4.17 and 3.2. Reverse transcriptase PCR was conducted to generate cDNA. The cDNA encoding the variable heavy and light chains was specifically amplified using PCR. The variable heavy chain region was cloned into an IgG1 expression vector. This vector was generated by cloning the constant domain of human IgG1 into the multiple cloning site of pcDNA3.1+/Hygro (Invitrogen, Burlington, ON). The variable light chain region was cloned into an IgK expression vector or Igλ. These vectors were generated by cloning the constant domain of human IgK or Igλ into the multiple cloning site of pcDNA3.1+/Neo

(Invitrogen, Burlington, ON). The heavy chain and the light chain expression vectors were then co-lipofected into a 60 mm dish of 70% confluent human embryonal kidney 293 cells and the transfected cells were allowed to secrete a recombinant antibody with the identical specificity as the original plasma cell for 24-72 hours. The supernatant (3 mL) was harvested from the HEK 293 cells and the secretion of an intact antibody was demonstrated with a sandwich ELISA to specifically detect human IgG. The specificity was assessed through binding of the recombinant antibody to TNFa using ELISA.

Generation of Anti-hTNFα Antibodies by XENOMAX®

Culture and selection of B cells

[0182] B-cells from the animals were harvested and cultured. Those secreting TNFa-specific antibodies were isolated as described in Babcook et al., *Proc. Natl. Acad. Sci. USA,* 93:7843-7848 (1996). ELISA was used to identify primary TNFa-specific wells. About 18 million B-cells were cultured from XENOMOUSE® animals in 480 96 well plates at 500 or 150 cells/well, and were screened on TNFa to identify the antigen-specific wells. 3,825 wells showed ODs significantly over background, a representative sample of which are shown in Table 11. Rabbit B-cells were also screened for their ability to secrete anti-TNFa antibodies and positives further assayed as described below.

Table 11

	Positives above cut off OD of:																
Plates ID's	>0	0.1	0.2	**0.3**	0.4	0.5	0.6	0.7	0.8	0.9	1	1.5	2	2.5	3	3.5	4
Plates 191-230	3840	3110	313	**158**	136	117	109	105	101	97	93	77	60	49	44	27	1
Plates 231-269	3744	2665	339	**167**	137	130	116	111	106	101	95	78	58	50	43	25	13
Total				**325**													

Normalization of antigen specific antibody concentrations

[0183] Using an ELISA method, supernatants for concentration of antigen specific antibody were normalized. Using an anti-target (TNFa) antibody of known concentration titrated in parallel, a standard curve can be generated and the amount of antigen specific antibody in the supernatant can be compared to the standard and it's concentration determined, see Table 12 below.

Table 12

	ELISA OD on Antigen				Extrapolated Concentration ng/mL *				
mab ID	1:40 dilution	1:80 dilution	1:160 dilution	1:320 dilution	Conc. At 1:40	Conc. At 1:80	Conc. At 1:160	Conc. At 1:320	Average
439A3	2.1	1.5	0.9	0.5		112	103	101	105
460A12	1.7	1.1	0.6	0.4		69	63		66
401A7	1.6	1.1	0.6	0.4		66	62		64
327D12	2.4	1.7	1.1	0.7			131	129	130
402G10	1.1	0.6	0.4	0.3	36	28			32
360A5	2.4	1.6	1.1	0.7			130	138	134
436F1	2.3	1.6	1.1	0.7			145	134	139
410F1	1.3	0.8	0.5	0.3	46	46			46
356B4	1.7	1.1	0.7	0.4		65	66		66
433F4	0.5	0.3	0.2	0.2	12				12
454G7	1.9	1.3	0.7	0.4		88	75		81

* Data points outside the linear region of the ELISA reader were excluded.

Limited antigen assay

[0184] The limited antigen analysis is a method that affinity ranks the antigen-specific antibodies prepared in B-cell culture supernatants relative to all other antigen-specific antibodies. In the presence of a very low coating of antigen, only the highest affinity antibodies should be able to bind to any detectable level at equilibrium. (*See, e.g.,* PCT Publication WO/03048730A2 entitled "IDENTIFICATION OF HIGH AFFINITY MOLECULES BY LIMITED DILUTION SCREENING" published on June 12, 2003).

[0185] Biotinylated TNFa was bound to streptavidin plates at three concentrations; 1ng/mL, 0.1ng/mL and 0.01ng/mL for 1 hour at room temperature on 96-well culture plates. Each plate was washed 5 times with dH_2O, before 45μL of 1% milk in PBS with 0.05% sodium azide were added to the plate, followed by 5μL of B cell supernatant added to each well. After 18 hours at room temperature on a shaker, the plates were again washed 5 times with dH_2O. To each well was added 50μL of Gt anti-Human (Fc)-HRP at 1μg/mL. After 1 hour at room temperature, the plates were again washed 5 times with dH_2O and 50μL of TMB substrate were added to each well. The reaction was stopped by the addition of 50uL of 1M phosphoric acid to each well and the plates were read at wavelength 450nm to give the results shown in Table 13.

Table 13

Well	1' Screen (OD)	Coating Concentrations		
		1ng/ml	0.1ng/ml	0.01ng/ml
401A7	2.92	1.94	0.33	0.19
433F4	2.96	1.12	0.24	0.20
337E7	2.53	0.97	0.47	0.19
164C7	1.97	0.81	0.24	0.16
356B4	2.87	0.69	0.17	0.15
402A4	2.33	0.61	0.35	0.18
286B9	2.56	0.32	0.32	0.27
203A2	2.33	0.23	0.15	0.19
286G8	2.06	0.21	0.19	0.19
286F11	2.93	0.18	0.23	0.19
286D12	0.78	0.18	0.21	0.25
286G1	0.82	0.17	0.16	0.18
286C4	0.75	0.17	0.17	0.19
286G6	0.97	0.16	0.18	0.14
287D1	0.58	0.16	0.19	0.16

Limited antigen analysis

[0186] B-cell culture supernatants were prepared having concentrations of antigen specific antibody ranging from 10ng/mL to 1000ng/mL. The results generated from limited antigen analysis were compared to a titration of 4.17 hybridoma derived antibody. In this assay many of the antibodies were not able to give detectable binding, however there were a number of wells including 401A7 and 433F4, which were clearly superior as measured by O.D. to the other culture supernatants and recombinant antibodies at all concentrations (Table 13). The remaining clones were further analyzed by combining the high antigen data which measures specific antibody concentration, (see above for details) and the limited antigen output. In this way it was possible to compare antibodies in B-cell culture supernatants to that of the control antibody over a concentration range as shown in Figure 2. Figure 2 is a point graph that compares the anti-TNFa limited antigen binding between antibodies in B-cell culture supernatants to that of a control antibody (4.17 IgG2) over a concentration range. The triangles represent the B-cell culture supernatant clones, and the blocks represent Bar Antibody (4.17 IgG2). B-cell culture supernatant clones with points above the bar antibody curve are ranked as having potentially higher affinity.

Neutralization of apoptosis by propidium iodide incorporation assay

[0187] All 1455 anti-hTNFa antibodies identified from B-cell culture well supernatants from foot-pad immunized mice were further assayed for their ability to neutralize the

biological effect of TNFa induced apoptosis on human MCF-7 cells. In addition, after limited antigen analysis of all 2,370 anti-hTNFa identified from BIP immunized animals, 145 antibodies having the highest kinetic ranking were further analyzed for neutralizing TNFa activity. 96 well plates were seeded at 5000 cells MCF-7/well, 200μL/well with phenol red free DMEM + 10% FCS. Plates were incubated overnight at 37°C + 5% CO_2. On each plate B-cell culture antibody supernatant was assayed along-side the most potent neutralizing anti-TNFa hybridoma antibodies, 4.17 and 3.2 and/or Rabbit 014 control in apoptosis medium (2.5% FCS, 5μg/mL CHX in phenol red free DMEM), at a constant concentration of 100 pg/mL (1.9 pM as a trimer) TNFa. Replicate wells with TNFa in apoptosis media and wells with apoptosis medium alone were included as controls. TNFa +/- test sample was pre-incubated for 1 hour at 37°C + 5% CO_2. 200μL TNFa +/- was transferred to cells and incubated overnight at 37°C + 5% CO_2.

[0188] Cells were stained with 0.5μg/mL PI and 2.5μg/mL Heochst 33342 for one hour. Percentage of apoptosis was determined by counting the number of dead cells (PI +ve) and dividing by the total number of cells (Heochst +ve). An example is show in Figure 3 which shows a representative bar graph that compares the effectiveness of various XENOMAX® B-cell culture supernatants at inhibiting TNFa induced cell apoptosis in human MCF-7 cells. A number of B-cell culture well supernatants showed the ability to neutralize TNFa induced apoptosis. These supernatants included: 164C7, 179B1, 401A7, 410B1, 439A3 and 460A12.

Neutralization potency determination of TNFa induced apoptosis by anti-hTNFa antibodies in polyclonal solutions

[0189] Using the extrapolated concentrations of antigen specific antibodies in polyclonal B-cell culture supernatants, the apparent potency of neutralization of TNFa induced apoptosis on MCF-7 cells was calculated. By performing the assay in parallel with a standard anti-target reagent, in this case the hybridoma derived antibody 3.2 IgG2, it was possible to set a potency bar and look for antibodies with higher potential potency than the standard.

[0190] An example of calculated potency comparisons for neutralization of TNFa induced apoptosis on MCF-7 cells is shown in Figure 4. Fig. 4 is a representative point graph that shows calculated potency comparisons for neutralization of TNFa induced apoptosis on human MCF-7 cells by XENOMAX® B-cell culture supernatants. The triangles represent the potency of B-cell culture supernatants, while the squares represent the potency of a bar control, 3.2 IgG2. A number of B-cell culture supernatants showed greater neutralization of TNFa induced apoptosis at lower anti-TNFa antibody concentrations than that of the 3.2 control standard curve, indicating greater potency.

Inhibition of TNFa binding to p55 (TNFa receptor I) by Rabbit Antibodies

[0191] Rabbit anti-TNFa neutralizing antibodies were found by examining whether or not the antibodies from the B-cell culture supernatants were able to inhibit TNFa binding to its p55 receptor. The following procedure was followed. 96 well microtiter plates were coated overnight with TNFa. The following day, the plates were washed and incubated +/- anti-TNFa antibodies for 1 hr. Biotin-p55 was then spiked into the plates for 1hr, washed with water and bound p55 was detected using Streptavidin-HRP. Plates were then washed and developed as done with other ELISAs described above. Antibodies which inhibited the binding of p55 were termed neutralizing, see Table 14.

Table 14

Abs	Assay 1	Assay 2
9C10	0.32	1.26
10G8	0.23	0.59
11A1	0.52	0.55
7A4	**0.08**	**0.39**
6A1	0.4	0.42
4A11	0.67	0.56
2A12	0.37	1.19
6A6	0.29	0.92
TNFa alone	0.3	0.97

TNFa-specific Hemolytic Plaque Assay

[0192] A number of specialized reagents were used to conduct this assay. These reagents were prepared as follows.

Biotinylation of Sheep red blood cells (SRBC)

[0193] SRBCs were stored in RPMI media as a 25% stock. A 250μL SRBC packed-cell pellet was obtained by aliquoting 1.0 mL of SRBC to a fresh eppendorf tube. The SRBC were pelleted with a pulse spin at 8000 rpm (6800 rcf) in microfuge, the supernatant drawn off, the pellet re-suspended in 1.0 mL PBS at pH 8.6, and the centrifugation repeated. The wash cycle was repeated 2 times, then the SRBC pellet was transferred to a 15-mL falcon tube and made to 5 mL with PBS pH 8.6. In a separate 50 mL falcon tube, 2.5mg of Sulfo-NHS biotin was added to 45 mL of PBS pH 8.6. Once the biotin had completely dissolved, the 5 mL of SRBCs were added and the tube rotated at RT for 1 hour. The SRBCs were centrifuged at 3000rpm for 5 min and the supernatant drawn off. The Biotinylated SRBCs were transferred to an eppendorf tube and washed 3 times as above but with PBS pH 7.4 and then made up to 5 mL with immune cell media (RPMI 1640) in a 15 mL falcon tube (5% B-SRBC stock). Stock was stored at 4° C until needed.

Streptavidin (SA) coating of B-SRBC

[0194] 1 mL of the 5% B-SRBC stock was transferred into a fresh eppendorf tube. The B-SRBC cells were washed 3 times as above and resuspended in 1.0 mL of PBS at pH 7.4 to give a final concentration of 5% (v/v). 10μL of a 10mg/mL streptavidin (CalBiochem, San Diego, CA) stock solution was added and the tube mixed and rotated at RT for 20min. The washing steps were repeated and the SA-SRBC were re-suspended in 1 mL PBS pH 7.4 (5% (v/v)).

Human TNFa coating of SA-SRBC

[0195] The SA-SRBCs were coated with biotinylated-TNFa at 10μg/mL, mixed and rotated at RT for 20 min. The SRBC were washed twice with 1.0 mL of PBS at pH 7.4 as above. The TNFa-coated SRBC were re-suspended in RPMI (+10%FCS) to a final concentration of 5% (v/v).

Determination of the quality of TNFa-SRBC by immunofluorescence (IF)

[0196] 10μL of 5% SA-SRBC and 10μL of 5% TNFa-coated SRBC were each added to a separate fresh 1.5 mL eppendorf tube containing 40μL of PBS. A control human anti-TNFa antibody was added to each sample of SRBCs at 45μg/mL. The tubes were rotated at RT for 25 min, and the cells were then washed three times with 100μL of PBS. The cells were re-suspended in 50μL of PBS and incubated with 40 μg/mL Gt-anti Human IgG Fc antibody conjugated to Alexa488 (Molecular Probes, Eugene, OR). The tubes were rotated at RT for 25 min, and then washed with 100μL PBS and the cells re-suspended in 10μL PBS. 10μL of the stained cells were spotted onto a clean glass microscope slide, covered with a glass coverslip, observed under fluorescent light, and scored on an arbitrary scale of 0-4.

Preparation of plasma cells

[0197] The contents of a single microculture well previously identified by various assays as containing a B cell clone secreting the immunoglobulin of interest were harvested. Using a 100-1000μL pipetman, the contents of the well were recovered by adding 37°C RPMI (10% FCS). The cells were re-suspended by pipetting and then transferred to a fresh 1.5 mL eppendorf tube (final vol. approx 500-700μL). The cells were centrifuged in a microfuge at 2500 rpm (660 rcf) for 1 minute at room temperature, then the tube was rotated 180 degrees and spun again for 1 minutes at 2500 rpm. The freeze media was drawn off and the immune cells resuspended in 100μL RPMI (10% FCS), then centrifuged. This washing with RPMI (10% FCS) was repeated and the cells re-suspended in 60μL RPMI (10% FCS) and stored on ice until ready to use.

Plaque assay

[0198] Glass slides (2 x 3 inch) were prepared in advance with silicone edges and allowed to cure overnight at RT. Before use the slides were treated with approx. 5μL of SigmaCoat (Sigma, Oakville, ON) wiped evenly over glass surface, allowed to dry and then wiped vigorously. To a 60μL sample of cells was added 60μL each of TNFa-coated SRBC (5% v/v stock), 4x guinea pig complement (Sigma, Oakville, ON) stock prepared in RPMI (10%FCS), and 4x enhancing sera stock (1:150 in RPMI (10%FCS)). The mixture -) was spotted (10-15μL) onto the prepared slides and the spots covered with undiluted paraffin oil. The slides were incubated at 37° C for a minimum of 45 minutes.

Plaque assay results

[0199] TNFa coated sheep red blood cells were used to identify antigen-specific plasma cells from the wells (see Table 15).

Table 15

mAb ID	Number of Single Cells picked	Single Cell Numbers
1F7	23	69
10F1	12	92
11A8	12	128
27A9	12	148
44G7	12	116
101F1	8	140
103H1	12	25
107A6	11	13
107G12	12	1
164C7	8	291
203A2	12	299
337E7	5	280
401A7	8	261
402G10	12	249
410F1	12	311
433F4	9	230
460A12	12	268

Expression of Recombinant anti-TNFa Antibodies

[0200] After isolation of the single plasma cells, mRNA was extracted and reverse transcriptase PCR was conducted to generate cDNA encoding the variable heavy and light chains. The human variable heavy chain region was cloned and isotype switched into an IgG1 expression vector. This vector was generated by cloning the constant domain of human IgG1 into the multiple cloning site of pcDNA3.1+/Hygro (Invitrogen, Burlington, ON). The human variable light chain region was cloned into an IgK expression vector. These vectors were generated by cloning the constant domain of human IgK into the multiple cloning site of pcDNA3.1+/Neo (Invitrogen, Burlington, ON). The heavy chain and the light chain expression vectors were then co-lipofected into a 60 mm dish of 70% confluent human embryonal kidney 293 cells and the transfected cells were allowed to secrete a recombinant antibody with the identical specificity as the original plasma cell for 24-72 hours. The supernatant (3 mL) was harvested from the HEK 293 cells and the secretion of an intact antibody was demonstrated with a sandwich ELISA to specifically detect human IgG (Table 16). Specificity was assessed through binding of the recombinant antibody to TNFa using ELISA.

Table 16

Supernatant ID	Titer	
	total antibody	antigen binding
11A8	>1:64	>1:64
27A9	1:16	1:64
103H1	>1:64	1:64
107A6	>1:64	>1:64
107G12	>1:64	>1:64
164C7	>1:64	>1:64
203A2	>1:64	>1:64
401A1	>1:64	>1:64
402G10	>1:64	>1:64

[0201] The secretion ELISA tests were performed as follows. Control plates were coated with 2mg/mL goat anti-human IgG H+L overnight as for binding plates, hTNFa was coated onto Costar Labcoat Universal Binding Polystyrene 96 well plates and held overnight at 4°C. The plates were washed five times with dH_2O. Recombinant antibodies were titrated 1:2 for 7 wells from the undiluted minilipofection supernatant. The plates were washed five times with dH_2O. A goat anti-human IgG Fc-specific HRP-conjugated antibody was added at a final concentration of 1μg/mL for 1 hour at RT for the secretion and the two binding assays. The plates were washed five times with dH_2O. The plates were developed with the addition of TMB for 30 minutes and the

ELISA was stopped by the addition of 1 M phosphoric acid. Each ELISA plate was analyzed to determine the optical density of each well at 450 nm.

[0202] Rabbit antibody genes were rescued, cloned and expressed as above, but were cloned into vectors containing rabbit IgG1 heavy constant or kappa constant regions. Cells from well 7A4 (Table 14) were isolated, cloned and expressed as a fully rabbit antibody, R014 (AB-TNFa-R014).

Purification of Recombinant Anti-TNFa Antibodies

[0203] For larger scale production, heavy and light chain expression vectors (2.5μg of each chain/dish) were lipofected into ten 100 mm dishes that were 70% confluent with HEK 293 cells. The transfected cells were incubated at 37°C for 4 days, the supernatant (6 mL) was harvested and replaced with 6 mL of fresh media. At day 7, the supernatant was removed and pooled with the initial harvest (120 mL total from 10 plates). Each antibody was purified from the supernatant using a Protein-A Sepharose (Amersham Biosciences, Piscataway, NJ) affinity chromatography (1 mL). The antibody was eluted from the Protein-A column with 500 mcL of 0.1 M Glycine pH 2.5. The eluate was dialysed in PBS pH 7.4 and filter sterilized. The antibody was analyzed by non-reducing SDS-PAGE to assess purity and yield. Concentration was also measured by UV analysis at OD 250.

EXAMPLE 4

BINDING OF ANTI-TNFa ANTIBODIES TO TRANSMEMBRANE TNFa

[0204] Both soluble and membrane-bound TNFa can interact with TNFa receptors and contribute to TNFa pro-inflammatory effects. Therefore, it was important to establish whether 299v2 and 263 can effectively bind to membrane-bound TNFa, in addition to the soluble version of the molecule. To this end, TNFa-transfected CHO cells were used as well as activated T cells.

[0205] Binding of anti-TNFa reagents to transmembrane mutant TNFa expressed on the surface of CHO cells was measured. Specifically, purified, quantitated IgG2 kappa and lambda hybridoma antibodies as well as isotype switched hybridoma and XENOMAX® derived IgG1 recombinant antibodies were assayed for their ability to bind transmembrane TNFa expressed on the surface of Chinese hamster ovary cells, CHO's. TNFa cDNA was mutated at various positions to prevent cleavage of TNFa from the surface of cells. The cDNA was then cloned into an expression vector. CHO cells were transfected and stable expressing cells were placed under drug selection to generate a DTNFa cell line. Anti-TNFa antibodies, as well as Etanercept, were titrated and added to DTNFa CHO cells on ice for 1 or 18 hours. Cells were washed in cold PBS and a secondary biotinylated anti-rabbit or human IgG was further incubated on ice for 10 minutes, washed and a tertiary SA-PE labeled antibody was added on ice for an additional 10 minutes.

Fluorescence activated cell sorting (FACS) was used to determine binding and staining profiles with antibodies at various concentrations.

[0206] At low concentrations, the human antibodies, as well as chimeric Infliximab and rabbit R014, bound the transmembrane form of TNFa on cells, whereas Etanercept clearly showed a lower binding signal. 299v2, 263, Infliximab, Adalimumab and Etanercept were incubated 18 hours at 4 degrees C on the DTNF-CHO cells at 0.1 ug/mL. With reference to the monoclonal antibodies, 299v2 and adalumimab apparently stained less than 263 and infliximab. The resulting data suggests that Fc mediated effects such as antibody-dependant cytotoxicity (CDC) and antibody-dependant cellular cytotoxicity (ADCC) should be observed on cells expressing transmembrane TNFa. A number of the generated antibodies can have more potent Fc mediated effects than Infliximab and Etanercept. This may be of particular benefit for the treatment of diseases where cell surface TNFa may play a patho-physiological role such as Crohn's or psoriasis.

[0207] For the treatment of disease indications where soluble forms of TNFa may mediate the majority of the disease state, an antibody with low Fc mediated effector function may be desirable. This could be achieved by expressing the anti-TNFa antibody as an IgG2 or IgG4 isotype.

[0208] Binding of anti-TNFa reagents to activated PBMC was also measured. PBMCs were isolated from a normal donor and incubated with an anti-CD3 antibody to activate T cells. T cell activation implies surface TNFa expression of membrane-bound TNFa. The ability of anti-TNFa reagents to bind to membrane-bound TNFa was again assessed at various concentrations by FACS analysis, gating on lymphocytes on the ground of light scattering and using a PE-conjugated anti-human IgG secondary antibody. The resulting staining data indicated that all the monoclonal antibodies 299v2, 263, Infliximab and adalumimab stained lymphocytes after T cell activation, while Etanercept does not. No anti-TNFa antibody stained lymphocytes if they were not subjected to T cell activation.

EXAMPLE 5

EPITOPE BINNING ASSAYS

Epitope mapping of anti TNFa Antibodies

[0209] The following describes the method used to map epitopes of anti TNFa Antibodies. Chimeric TNFa proteins, using human and mouse TNFa, were constructed and expressed. An alignment of human and mouse TNFa is provided in Table 17.

Table 17

Human: VRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANA
Mouse: LRSSSQNSSDKPVAHVVANHQVEEQLEWLSQRANA

Human: LLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCP
Mouse: LLANGMDLKDNQLVVPADGLYLVYSQVLFKGQGCP

Human: STHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRE
Mouse: DY-VLLTHTVSRFAISYQEKVNLLSAVKSPCPKD

Human: TPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINR
Mouse: TPEGAELKPWYEPIYLGGVFQLEKGDQLSAEVNL

Human: PDYLDFAESGQVYFGIIAL SEQ ID NO:265
Mouse: PKYLDFAESGQVYFGVIAL SEQ ID NO:266

[0210] Restriction cleavage sites common in human and murine TNFa-a genes were used for construction of in-frame fusion TNFa chimeric proteins. Seven constructs were made: human TNFa, mouse TNFa, H/M BglI, M/H BglI, H/M HincII, H/M PvuII, M/H PvuII. All proteins were expressed and secreted in detectable levels measured by an ELISA assay using polyclonal antibodies against human and mouse TNFa. Chimeric TNFa proteins: the amino acid joining points are at positions: BglI- 36/37, HincII-90/92, PvuII – 124/126. The difference on one amino acid in the last two cases is due to the absence of the histidine residue at position 73 in the murine TNFa sequence. An example of anti-TNFa antibodies binding to these proteins by ELISA is in Table 18.

Table 18

Construct	Goat Anti-Mouse	Goat Anti-human	3.2 Ab	3.7 Ab	4.17 Ab	Human residues
H-TNFa	+	+++	+	+	+	1-157
M TNFa	+	+	-	-	-	None
H/MBgl1	++++	+++	-	-	+ 1-36	1-36
M/HuBgl1	+	+++	-	+ 36-157	-	36-157
Hu/M PVu11	+	+++	+	-	+	1-125
M/Hu PVu11	++	+	-	-	-	125-157
Hu/M Hin C l1	+	++++	++ 1-91	-	++	1-91

[0211] In order to define the binding site for different antibodies, a number of residues of hTNFa were mutated using site directed mutagenesis. A panel of antibodies was screened for

binding by an ELISA assay. Human residues were replaced with the murine residues at position 27, 31, and 131. Histidine at position 73 was deleted, an example is illustrated in Table 19.

Table 19

Human Amino acid residues	1-36	36-157	1-125	1-91	1-157	R31Q mut	R31Q, Q27E mut	R131Q mut	His 73del
250Ab	-	-	-	-	+++	+++	+++	+++	+++
263Ab	-	-	-	-	+++	+++	+++	+++	+++
269Ab	-	-	-	-	+++	+++	+++	+++	+++
282 Ab	-	--	-	-	+++	+++	+++	+++	+++
283 Ab	-	-	-	-	+++	+++	+++	+++	+++
291 Ab	+++	-	+++	+++	+++	--	-	+++	+++
299v2Ab	+++	--	+++	+++	+++	-	-	+++	+++
313 Ab	+++	-	+++	+++	+++	-	-	+++	+++
Infliximab	-	-	-	-	+++	+++	+++	+++	+++
3.2.1	-	-	++	++	-	++	++	+++	+++
3.7.1	-	++	-	-	-	++	++	+++	+++
4.17.1	++	-	++	++	-	+	-	+++	+++
Rabbit R014	+++	-	+++	+++	+++	+++	+++	+++	+++

[0212] As illustrated by Table 19, the binding site for Rabbit 014, 4.17, SC291, SC299 and SC313 are located in the first 36 amino acid residues of human TNFa. Amino Acids 31-35 have been shown to be involved in receptor recognition and triggering of biological response (Jones, E.Y., Stuart, D.I., and Walker, NPC., (1992) in Tumor Necrosis Factors: Structure, Function and Mechanism of Action (Aggarwal, B.B., and Vilcek, J., eds) pp 93-127, Marcel Dekker, Inc., New-York a non-conservative change of Arg31 was introduced for further epitope mapping. The single amino acid change at position 31 was shown to knock out the binding of SC291, SC299 and SC313 completely, while mAb 4.17 lost only 80% of its binding activity, an additional change at position 27 was required for the block the activity of 4.17.

[0213] The Binding site of MAb 3.2. lies between residues 1-91. Although replacement of Gln27 and arg31 did not affect its binding to human TNFa, the N-terminus appears to be necessary for its binding activity. Mab 3.7 epitope lies between residues 36-157.

[0214] None of the chimeras could be neutralized using monoclonal antibodies SC250, SC263, SC269, SC282, SC283 and Infliximab. All these antibodies are highly specific for human TNFa, and their epitope is a constellation of residues located in a different, non contiguous position

of the TNFa polypeptide. Gln27, Arg31, His73 and Arg131 are not involved in the neutralizing binding site.

[0215] Table 20 summarize the results of additional epitope mapping performed on 299v2, 263, etanercept, infliximab and Adalimumab. As shown in the Table 20, 299v2, etanercept, and adalimumab bind to the chimeric proteins containing the region of human TNF between aa 1 and aa 36, while 263 and infliximab do not bind any of the chimeric proteins. All the anti-TNF antibodies bind to human TNF, but none to murine TNF. These results indicate that the binding regions of 299v2, etanercept, and adalimumab are most likely comprised within the first 36 aa of TNF, while those of 263 and infliximab are scattered over the entire molecule. All anti-TNF antibodies bind protein-denaturation sensitive regions, indicating that their binding regions are conformational.

Table 20

Human aa Residues **Murine aa Residues**	**1-36** **37-157**	**1-91** **92-157**	**1-125** **126-157**	**36-157** **1-35**	**125-157** **1-125**	**1-157** **-**	**-** **1-157**
Etanercept	+	+	+	-	-	+	-
299v2	+	+	+	-	-	+	-
Adalimumab	+	+	+	-	-	+	-
Infliximab	-	-	-	-	-	+	-
263	-	-	-	-	-	+	-

[0216] The TNFa receptors p75-hFc and p55-hFc (Catalog number 372-RI-050 and 372-RI/CF from R&D) were further analyzed for binding to TNFa proteins as shown in Table 21.

Table 21

Constructs	p55-hFc	p75s-hFc	Human amino acid residues
Hu TNFa	++	++	1-157
Hu/MBgl1	++	++	1-36
M/HuBgl1	-	-	36-157
Hu/M PVu11	+	++	1-125
Hu/M Hin C l1	++	++	1-91
M/Hu Hin CII	++	++	91-157

EXAMPLE 6

ANTI-MACAQUE TNFa BINDING CROSS-REACTIVITY

Binding to human and monkey soluble recombinant TNFa

[0217] Anti-TNFa antibodies were also tested for their ability to bind to soluble recombinant TNFa. Human and monkey (cynomolgous macaque) TNFa were expressed in *E. coli* as fusion proteins with GST. Binding was assessed by ELISA. 299v2, 263, etanercept, infliximab, and adalumimab ("anti-TNFa antibodies") were incubated in 96-well plates coated overnight with 0.5 μg/ml of human GST-TNFa, 2 μg/ml of monkey GST-TNFa, and 10 μg/ml of GST. Bound antibody was detected using an HRP-conjugated goat anti-human IgG antibody. Results showed that anti-TNFa antibodies all bind to human TNFa with a similar dose-response (Figure 5). Anti-TNFa antibodies differently bind to monkey TNFa. While 299v2, etanercept, and adalumimab bind cynomolgus macaque TNFa in a similar fashion, 263 and infliximab appear not to bind to cynomolgous macaque TNFa (Figure 6).

EXAMPLE 7

KINETIC ANALYSIS

[0218] The kinetic measurements of the anti-TNFa antibodies were evaluated using KinExA® and BIACORE® technologies. The KinExA® method involves solution-based determination of formal affinity measurements at equilibrium. To measure the binding kinetics of each human anti-TNFa antibody, two experiments in replicates of three were performed. In both experiments a known concentration of antigen was titrated and a different antibody concentration was added to each antigen titration and allowed to reach binding equilibrium. To determine the K_d measurements on human TNFa, the K_d was calculated using a molar TNFa binding site concentration of one trimer (52.5 kDa), see Table 22, or three monomers (17.5 kDa), see Table 23. The results were analyzed by dual curve analysis. Kinetic measurements for the rabbit R014 antibody were essentially performed as above, however, the unknown antigen concentration method was performed using the known antibody concentration to calculate the K_d. In addition, to negate the possibility of avidity effects, Fab fragments were generated by papain cleavage and the kinetic analysis was repeated (see Table 24).

[0219] Additional kinetic constants were also calculated from BIACORE® data using the methods described in their product literature. An association rate constant (k_a) is the value that represents strength (extent) of binding of an antibody with target antigen as calculated based on antigen-antibody reaction kinetics. A dissociation rate constant (k_d) is the value that represents the strength (extent) of dissociation of this monoclonal antibody from target antigen as calculated based on antigen-antibody reaction kinetics. The dissociation constant (K_d) is the value obtained by dividing the dissociation rate constant (k_d) value from the association rate constant (k_a), see Table 25.

Table 22

Ab	K_d (M)	K_d (M) High	K_d (M) Low	% Error
299 V1	6.3 e-13	9.2 e-13	4.3 e-13	4.99
299v2	1.07 e-12	SD=0.48 (n=5)		
263	3.73 e-12	SD=1.06 (n=4)		
3.2	4.77 e-12	7.6 e-12	2.43 e-12	4.7
p75-hFc*	4.10 e-13	SD=0.15 (n=4)		>5%**
Infliximab	4.70 e-12	6.90 e-12	2.93 e-12	5.45
Adulimumab	3.90 e-12	6.87 e-12	1.64 e-12	5.77

*A p75-hFc construct (R&D Systems) similar to etanercept (Enbrel) was used in these studies. When etanercept was used similar results were obtained (data not shown).
** Each experiment had errors between 6-7%.

Table 23

mAb	K_d (M)	K_d (M) High	K_d (M) Low	% Error
299 V1	1.89 e-12	2.76 e-12	1.29 e-12	4.99
299v2	3.20 e-12	SD=1.44 (n=5)		
263	1.12 e-11	SD=3.17 (n=4)		
3.2	1.43 e-11	2.30 e-11	7.30 e-12	4.7
p75-hFc*	1.23 e-12	SD=0.44 (n=4)		>5%**
Infliximab	1.41 e-11	2.07 e-11	8.78 e-12	5.45
Adulimumab	1.17 e-11	2.06 e-11	4.94 e-12	5.77

*A p75-hFc construct (R&D Systems) similar to etanercept (Enbrel) was used in these studies. When etanercept was used similar results were obtained (data not shown).
** Each experiment had errors between 6-7%.

Table 24

mAb	K_d (M)	K_d (M) High	K_d (M) Low	% Error
Rabbit R014	7.87 e-13	2.47 e-12	1.56 e-13	2.74
Rabbit R014 Fab	6.38 e-13	1.94 e-10	2.09 e-15	16.9

Table 25

mAb 299 v2	Average	Standard Deviation (CV)	95% Confidence Intervals
k_a ($M^{-1}s^{-1}$)	2.16×10^6 (N=5)	$+/- 9.38 \times 10^5$ (46%)	$+/- 1.22 \times 10^6$ (56%)
k_d (s^{-1})	1.03×10^{-5} (N=5)	$+/- 5.48 \times 10^{-6}$ (53%)	$+/- 6.81 \times 10^{-6}$ (66%)
K_d (pM)	5.7	+/- 3.9 (68%)	+/- 4.8 (84%)

[0220] The binding affinity of 299v2 for cynomolgus macaque TNFa was also measured, since this antibody had been found capable of binding monkey TNFa in an ELISA. The KinExA method was also used to measure the K_d describing this binding affinity. 299v2 bound to monkey TNFa with an affinity of 626 pM, considering TNFa as a monomer, which is therefore approximately 200 times lower than the affinity for human TNFa.

EXAMPLE 8

IN VITRO ANTI-HTNFa ANTIBODIES CHARACTERIZATION.

Inhibition of TNFa induced apoptosis on human MCF-7 cells.

[0221] IgG2 kappa and lambda hybridomas were bulk cultured, purified and quantified as described previously. Isotype switched hybridoma and XENOMAX® derived IgG1 recombinant antibodies were expressed, purified and quantitated as described previously. Antibodies were further assayed for their ability to neutralize the biological effect of TNFa induced apoptosis on human MCF-7 cells. 96-well plates were seeded at 5000 cells MCF-7/well, 200µL/well with phenol red free DMEM + 10% FCS. The plates were incubated overnight at 37°C + 5% CO_2. On each plate, a titration of each antibody was assayed, in final concentrations from 0.005 ng/ml to 10 µg/ml. Anti-TNF reagents were diluted in apoptosis medium (2.5% FCS, 5µg/mL CHX in phenol red free DMEM), in triplicate or up to replicates of six, at a constant concentration of 100 pg/mL (1.9 pM as a trimer) TNFa. 6 well plates with TNFa alone in apoptosis media and 6 well plates with apoptosis medium alone were also included. TNFa +/- neutralizing antibody was pre-incubated for 1 hour or for 18 hours at 37°C + 5% CO_2. 200µL TNFa +/- neutralizing antibody was transferred to cells and incubated overnight at 37°C + 5% CO_2.

[0222] Cells were stained with 0.5µg/mL PI and 2.5µg/mL Heochst 33342 for one hour. Percentage of apoptosis was determined by counting the number of dead cells (PI +ve) and dividing by the total number of cells (Heochst +ve). Neutralization was assayed using MCF-7 cells and detected as a ratio of propidium iodide and Heochst 33342 staining. An example of neutralizing antibody titration curves used to generate IC_{50} values by four parameter curve fitting is provided in Figures 7 and 8, as line graphs.

[0223] Results shown in Table 26 are the averages of data obtained from different experiments of in vitro inhibition of TNF induced apoptosis in MCF-7 cells at a 1 hour or 18 hour antibody pre-incubation time point with TNF. The longer 18 hour preincubation may allow affinity differences to be seen more readily, as antibody-antigen binding is nearer to equilibrium. 299v2 demonstrated the lowest IC50s of any of the fully human mAbs as well as Infliximab. A strong correlation between affinity and neutralization potency is also observed.

Table 26

mAb	IC50 1hr Pre-incubation (pM)		IC50 18hr Pre-incubation (pM)	
	Average	St. Dev.	Average	St. Dev.
299v2	18.6	4.2	1.6	1.3
263	59.5	13.4	37.0	4.3

4.17 g1	256.3	238.8	40.4	6.2
3.2 g1	93.8	11.0	38.6	12.1
Infliximab	32.4	1.5	31.7	20.4
Adalimumab	75.8	12.8	34.5	8.3
Etanercept	3.4	1.8	2.2	0.8

[0224] An example of the average IC_{50} values for anti-TNFa neutralization of apoptosis is represented in Figure 9, a bar graph. As Figure 9 indicates, all antibodies are potent neutralizers of TNFa induced apoptosis. In particular, antibody 299v2 appears to have a better average potency than Infliximab, Adalimumab or Etanercept.

[0225] Table 27 shows the inhibition of TNF induced apoptosis on MCF-7 cells by the rabbit R014 mAb after 1 hour pre-incubation with TNF.

Table 27

Anti-TNFa	**Average IC_{50}(pM)**	**SD (pM)**	***n=**
RO14	14.2	4.5	12

* number of experiments

Inhibition of TNFa induced apoptosis on human WM 266.4 cells.

[0226] IgG2 kappa and lambda hybridomas were bulk cultured, purified and quantified as described above. Isotype switched hybridoma and XENOMAX® derived IgG1 recombinant antibodies were expressed, purified and quantitated as above. Antibodies were further assayed for their ability to neutralize the biological effect of TNFa induced apoptosis on human WM 266.4 cells. 20,000 WM266.6 cells were plated in 96-well plates in complete media (RPMI1640/10%FBS/Gln/P/S) and incubated at 37°C/10% CO_2 overnight. Media was removed and 50µL test antibodies plus TNFa (pre-incubated for 30' at room temperature) was added in serum free media (RPMI1640/Gln/P/S). 50µL cyclohexamide plates were incubated overnight as above final assay conditions: V=100µL, cyclohexamide = 6µg/mL, TNFa = 600 pg/mL = 11.4 pM as a trimer. Test antibodies concentrations vary as described. 100µL Caspase buffer and 0.3µL Caspase substrate (APO-ONE, Promega) were added per well. Caspase activity was determined on the Victor Wallac; excitation wavelength @ 485 nm; emission wavelength @ 530 nm. An example of the antibodies ability to neutralize apoptosis by is shown in Figure 10. Fig. 10 is a bar graph that shows the average IC_{50} values for anti-TNFa neutralization. Neutralization was performed on human WM266 cells and caspase activity was measured as an indication of TNFa induced

apoptosis. Antibody IC_{50} calculations were performed as described in the brief description of Figure 7.

[0227] A control shows induction of apoptosis by TNFa and cyclohexamide alone. Other controls included Rabbit 014 Ab as well Infliximab and p75-hFc (R&D), as an Etanercept surrogate. The graph shows caspase activity as a measure of TNFa induced apoptosis. As can be seen in Figure 10, SC299V1 and SC299V2 antibodies are consistently similar to each other and in addition to R014, 263 and perhaps 234 are more potent than Infliximab and p75-hFc. 4.17 IgG2, SC282 and 3.2 IgG2 were more potent than p75-hFc. As also indicated by Figure 10, all antibodies are potent neutralizers of TNFa induced apoptosis.

Inhibition of TNFa-induced IL-8 production in human whole blood.

[0228] Cultures of human whole blood reproduce naturally occurring conditions of clinical relevance that may not be present in cell cultures or in experimental animals. Whole blood cultures were used to assess the efficacy of anti-TNFa antibodies to neutralize TNFa-induced IL-8 production. Whole blood was obtained from normal donors by venopuncture, collected in EDTA tubes, and plated into 96-well plates. Anti-TNFa antibodies were diluted in RPMI medium and mixed with the whole blood. An irrelevant human IgG1 antibody was used as a control. This was followed by the addition of TNFa (final concentration 100 pg/ml, corresponding to 1.9 pM considering TNFa as a trimer). Plates were then incubated for 6 hours at 37°C. After incubation, Triton X-100 was added to the cultures at a final concentration of 0.5% v/v to cause cell lysis. IL-8 production was measured in the by ELISA. To express results, IL-8 induced by TNFa in the presence of the IgG1 control was set as 100%. Table 28 reports the IC50s for the anti-TNFa antibodies calculated using inhibition curves (Fig 11). 299v2 and the Etanercept surrogate demonstrate the lowest IC50s and highest potencies.

Table 28

	Whole Blood IC50 (pM)
299v2	131 ± 9
263	524 ± 60
Infliximab	546 ± 65
Adalimumab	896 ± 159
p75-hFc*	166 ± 32*

*A p75-hFc construct (R&D Systems) similar to etanercept (Enbrel) was used in these studies. When etanercept was used similar results were obtained (data not shown).

Antibody-dependent cell-mediated cytotoxicity

[0229] Anti-TNFa antibodies were assayed to determine their ability to support the killing of TNFa-transfected CHO cells mediated by PBMCs, mainly NK cells. Briefly, human PBMCs were obtained from a normal donor and resuspended at a concentration calibrated so that, added to the effector cells, would yield 1:100 effector/target cell ratios. At the same time, TNFa-transfected CHO cells, that stably express membrane-bound TNFa, were labeled with the membrane dye PKH-26. CHO cells were then seeded into 96-well dishes in triplicate with or without 5 μg/ml antibody. After a 30 min incubation, effector cells were added, and the ADCC reaction was allowed to occur overnight at 37°C. At this point, triplicate samples were pooled, stained with the dye TOPO-3 per manufacturer's instruction, and analyzed by FACS. Ratios of the number of PKH-26 and TOPO-3 double-positive cells (dead target cells) versus PKH-26 single-positive cells (live target cells) were calculated and used to express results as percentages. The results indicate that the monoclonal antibodies have the ability to support ADCC at remarkable variance with p75-hFc, that was used as etanercept surrogate (Table 29).

Complement-dependent cytotoxicity

[0230] Anti-TNFa antibodies were also assayed for the ability to fix complement and thus mediate the killing of TNFa-transfected CHO cells. Briefly, CHO cells were seeded at 125000/well in 96-well plates and added with 5 μg/ml antibody in duplicate. After 3 hours of incubation on ice, rabbit complement was added to a final concentration of 10%, and the CDC reaction was allowed to occur for 30 min at room temperature. At this point, cells were stained with 0.5 μg/ml of PI and 2.5 μg/ml of Heochst 33342 for 1 hour and counted using Autoscope. Experiments were conducted in triplicate. Results were calculated and expressed as described above for the TNFa-induced apoptosis assay. As in the case of ADCC, the results indicate that the monoclonal antibodies have ability to incite CDC at variance with p75-hFc, that was used as etanercept surrogate (Table 29).

Table 29

	ADCC (%)	CDC (%)
IGg1 Ctrl	2 ± 2	2 ± 0
299v2	16 ± 5	9 ± 1
263	10 ± 5	17 ± 0
Infliximab	15 ± 5	12 ± 2
Adalimumab	8 ± 4	12 ± 1
p75-hFc *	2 ± 1	2 ± 2

**A p75-hFc construct (R&D Systems) similar to etanercept (Enbrel) was used in these studies.

EXAMPLE 9

IN VIVO ANTI-HTNFa ANTIBODIES CHARACTERIZATION.

Inhibition of TNFa-induced hepatic injury in mice

[0231] To test whether anti-human TNFa antibodies neutralize human TNFa *in vivo*, the ability of anti-human TNFa antibodies to protect against the hepatic injury induced by human TNFa and D-galactosamine (D-GalN) administration in mice was studied (Lehmann V et al., *J. Exp. Med.*, 1987 165(3): 657-63). Administration of TNFa with D-GalN induces fulminant liver injury that resembles the liver injury induced by LPS and D-GalN, characterized by widespread apoptotic death of hepatocytes, ultimately resulting in shock and lethality. D-GalN treatment renders mice 100-1000 more sensitive to the lethal effects of lipopolysaccharide (LPS) as well as murine TNFa (Lehmann V, et al., *J. Exp. Med.*, 1987 165(3): 657-63). The apoptotic liver injury induced by LPS and D-GalN has been shown to be dependent on endogenously produced TNFa (Leist M, et al., *Am. J Pathol.*, 1995, 146(5): 1220-34.). It has also been demonstrated that this liver injury is dependent exclusively on secreted TNFa signaling through the p55 receptor (Nowak M, et al., *Am. J. Physiol.* 2000, 278(5): R1202-9), suggesting that D-GalN also sensitizes to the lethal effects of human TNFa, which in mice binds only p55 TNFa receptor. Liver injury induced by hTNFa and D-GalN was assessed by measuring serum enzyme activity of alanine aminotransferase (ALT).

[0232] The experiments were performed as described. 8 to 10 weeks old Balb/c female mice, weighing approximately 20 g, were obtained from Charles River Laboratories. 8-10 mice per group were used. The dose and route of administration as well as the time for measuring the ALT levels in the serum were defined in preliminary experiments. Mice were injected with D-GalN (Sigma) (900mg/kg, ip) 90 min before human TNF (R&D System) (1 μg/mouse, iv). The intravenous administration of 1 μg/mouse of TNF resulted in circulating levels of TNF of 19 nM (considering TNF as a trimer). Hepatocyte damage was assessed 6 hours after TNF/ GalN administration by measuring ALT using a commercial diagnostic kit (Sigma). To compare the ability of 299v2, 263, Etanercept, Adalimumab and infliximab to inhibit TNFa in vivo, dose-response experiments were performed by injecting anti-TNF reagents (1-10 i.v. μg/mouse) 90 min before TNF (1 μg/mouse, iv). Control mice received saline before TNF. Data were expressed as % of control and neutralization curves were generated (Figure 12). IC50s were calculated using a four parameter fit curve. Table 30 shows the IC50s for the different anti-TNF reagents averaged from different experiments.

Inhibition of TNFa-induced IL-6 production in mice

[0233] As another approach to testing the ability of anti-TNFa antibodies to inhibit TNFa *in vivo*, anti-TNFa antibodies were used to block the production of IL-6 induced in mice by human. TNFa engenders many acute biological actions, including the induction of IL-6 (Benigni et al., J. Immunol. 157:5563, 1996). 8-10 mice per group were used. As initially established in time-course experiments, injection of human TNFa into mice causes a rapid rise in serum IL-6 levels that peak at 2 hours after injection. Based on the results of other preliminary experiments aimed to define the dose and the route of administration of TNFa, mice were injected intravenously with 1 μg/mouse of human TNFa. IL-6 levels were measured 2 hours after TNFa administration using a commercial ELISA kit (R&D System). Dose-response experiments were performed by injecting anti-TNFa antibodies (1-10 i.v. μg/mouse) 90 min before TNFa (1 μg/mouse, iv). Control mice received saline before TNFa. Data were expressed as a percentage of control and neutralization curves were generated (Fig. 13). IC50s were calculated using a four parameter fit curve. Table 30 shows the IC50s for the different anti-TNFa antibodies averaged from different experiments.

Table 30

	***In vivo* Potency (nM)**	
	ALT	**IL-6**
299v2	50 ± 4	43 ± 1
263	48 ± 6	35 ± 5
Infliximab	41 ± 10	43 ± 21
Adalimumab	40 ± 1	36 ± 5
Etanercept	27 ± 16	27 ± 14

EXAMPLE 10

STRUCTURAL ANALYSIS OF ANTI-TNFa ANTIBODIES

[0234] The variable heavy chains and the variable light chains for the antibodies shown in Table 1 above were sequenced to determine their DNA sequences. The complete sequence information for all anti-TNFa antibodies are shown in the sequence listing submitted herewith, including nucleotide and amino acid sequences.

[0235] Table 31 is a table comparing various XENOMAX® derived antibody heavy chain regions to a particular germ line heavy chain region. Table 32 is a table comparing various XENOMAX® derived antibody light chain regions to a particular germ line light chain region. Table 33 is a table comparing various hybridoma derived antibody heavy chain regions to a particular germ line heavy chain region. Table 34 is a table comparing various hybridoma derived antibody light chain regions to a particular germ line light chain region.

Table 31. Xenomax Heavy Chain Analysis

SEQ ID NO:	Single Cell	V Heavy/D/J	FR1	CDR1	FR2
267	-	**Germline**	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA
74	299 v. 2	VH3-33/D5-5/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDMH	WVRQAPGKGLEWVA
70	299 v. 1	VH3-33/D5-5/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDMH	WVRQAPGKGLEWVA
38	148	VH3-33/D5-5/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	NYDMH	WVRQAPGKGLEWVA
78	313	VH3-33/D5-24/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	NHDIH	WVRQAPGKGLEWVA
6	15	VH3-33/D6-6/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDIH	WVRQAPGKGLEWVA
22	95	VH3-33/D6-19/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	NYDMH	WVRQAPGKGLEWVA
268	-	**Germline**	EVQLVESGGGLIQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS
46	250	VH3-53/D3-16/JH4b	EVQLVESGGGLIQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS
50	263	VH3-53/D3-16/JH4b	EVQLVESGGGLIQPGGSLRLSCAASGFTVS	RNYMS	WVRQAPGKGLEWVS
54	269	VH3-53/D3-16/JH4b	EVQLVESGGGLIQPGGSLRLSCAASEFTVS	RNYMS	WVRQAPGKGLEWVS
269	-	**Germline**	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA
58	280	VH3-33/D4-17/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTVS	SYGMH	WVRQAPGKGLEWVA
62	282	VH3-33/D4-17/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTVS	SYGMH	WVRQAPGKGLEWVA
66	291	VH3-33/D1-26/JH6b	QVQLVESGGSVVQPGRSLRLSCAASGFTFS	NYGIH	WVRQAPGKGLEWVA
270	-	**Germline**	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA
42	234	VH3-30/D1-26/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDMH	WVRQAPGKGLEWVA
34	140	VH3-30/D1-20/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA
14	28	VH3-30/D3-3/JH6b	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	NYGMH	WVRQAPGKGLEWVT
271	-	**Germline**	QVQLQESGPGLVKPSETLSLTCTVSGGSIS	SYYWS	WIRQPAGKGLEWIG
18	69	VH4-4/D2-2/JH2	QVQLQESGPGLVKPSETLSLTCTVSGGSIN	HYYWS	WIRQPAGKGLEWIG
272	-	**Germline**	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG
2	2	VH4-31/D1-20/JH6b	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG
10	25	VH4-31/D1-20/JH6b	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG
30	131	VH4-31/D1-20/JH6b	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG
26	123	VH4-31/D1-20/JH6b	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG

SEQ ID NO:	Single Cell	CDR2	FR3	CDR3	FR4
267	-	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
74	299 v. 2	VIWSDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EVESAMGGFYYNGMDV	WGQGTTVTVSS
70	299 v. 1	VIWSDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EVESAMGGFYYNGMDV	WGQGATVTVSS
38	148	VIWYDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYFCAR	ETAILRGYYYYDMDV	WGQGTTVTVSS
78	313	VIWSDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EKMAIIKGYYYYGMDV	WGQGTTVTVSS
6	15	VIWYDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EEQLVRGGYYYYGMDV	WGQGTTVTVSS
22	95	VIWYDGSIKYYADSVKG	RFTISRDNSKNTLHLQMNSLRAEDTAVYYCAR	EIAVAGGYYYGLDV	WGQGTTVTVSS
268	-	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTLVTVSS
46	250	VIYSGDRTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GEGGFDY	WGQGTLVTVSS
50	263	VIYSGDRTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GEGGFDY	WGQGTLVTVSS
54	269	VIYSGDRTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GEGGFDY	WGQGTLVTVSS
269	-	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
58	280	VIWSNGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DNGVYVGYAYYYGMDV	WGQGTTVTVSS
62	282	VIWSNGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DNGVYVGYAYYYGMDV	WGQGTTVTVSS
66	291	VIWSDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ELPNSGSYSGYYYYYGMDV	WGQGTTVTVSS
270	-	VISYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
42	234	VISYDGSIKYYADSVKG	RFTISRDNSKNTLYLQVNSLRAEDTAVYYCAR	EVRSGSYYYYYSMDV	WGQGTTVTVSS
34	140	VISYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DQDNWNYYYGMDV	WGQGTTVTVSS
14	28	IISYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVT	YYDFWSGYLPGMDV	WGQGTTVTVSS
271	-	RIYTSGSTNYNPSLKS	RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR		WGRGTLVTVSS
18	69	RIYPTGSTNYNPSLKS	RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAG	GWSYWYFDL	WGRGTLVTVSS
272	-	YIYYSGSTYYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR		WGQGTTVTVSS
2	2	NIYYSGSTYYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	DSNQYNWNDEVYDYGLDV	WGQGTTVTVSS
10	25	NIYYSGSTYYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYCAR	DSNQYNWNDEVYDYGLDV	WGQGTTVTVSS
30	131	NIYYSGSTYYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	DSNQYNWNDEVYDYGLDV	WGQGTTVTVSS
26	123	NIYYSGSTYYTPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	DSNQYNWNDEVYDYGLDV	WGQGTTVTVSS

Table 32. Xenomax Light Chain Analysis

SEQ ID NO:	Single Cell	V Kappa/J	FR1	CDR1	FR2
273	-	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
72	299	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRIDLG	WYQQKPGKAPKRLIY
80	313	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
68	291	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
44	234	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQDIRNDLG	WYQQKPGKAPKRLIY
4	2	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
12	25	A30VK1/JK4	DIQMTQSPSSLSASVRDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
32	131	A30VK1/JK4	DIQMTQSPSALSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
8	15	A30VK1/JK4	DIQMTQSPSSLSASIGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
24	95	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
40	148	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIS
28	123	A30VK1/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
274	-	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
60	280	A30VK1/JK1	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
64	282	A30VK1/JK1	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY
16	28	A30VK1/JK1	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLT	WYQQKPGKAPKRLIY
275	-	**Germline**	DVVMTQSPLSLPVTLGQPASISC	RSSQSLVYSDGNTYLN	WFQQRPGQSPRRLIY
20	70	A1VK2/JK4	DVVMTQSPLSLPVTLGQPASISC	RSSQSLVYSDGSTYLN	WFQQRPGQSPRRLIY
276	-	**Germline**	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY
36	145	A19VK2/JK1	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIF
277	-	**Germline**	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY
48	250	L2VK3/JK1	EIVMTQSPATLSVSPGERATLSC	RASQSVTSNLA	WYQQKPGQAPRLLIH
52	263	L2VK3/JK1	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIH
56	269	L2VK3/JK1	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIH

SEQ ID NO:	Single Cell	CDR2	FR3	CDR3	FR4
273	-	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
72	299	AASTLQS	GVPSRFSGSGSGTEFIFTISSLQPEDFASYYC	LQHKSYPLT	FGGGTKVEIK
80	313	AASSLES	GVPSRFSGSGSGPEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIQ
68	291	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHCCYPLT	FGGGTKVEIK
44	234	AASSLQS	GVPSRFSGSGSGPEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4	2	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNNYPLT	FGGGTKVEIK
12	25	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
32	131	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHKSYPLT	FGGGTKVEIK
8	15	AASSLQS	GVPSRFSGSGSGPEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
24	95	AASSLQS	GVPSRFSGSGSGTEFTLTVSSLQPEDFATYYC	LQHHSYPLT	FGGGTKVQIN
40	148	AASSLQG	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
28	123	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNNYPLT	FGGGTKVEIK
274	-	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPWT	FGQGTKVEIK
60	280	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPRT	FGQGTKVEIK
64	282	AASSLHS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPWT	FGQGTKVEIK
16	28	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSFPWT	FGQGTKVEIK
275	-	KVWNWDS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGTHWP##LT	FGGGTKVEIK
20	70	KVWNWDS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGSHWPREFT	FGGGTKVEIK
276	-	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTWT	FGQGTKVEIK
36	145	LGSYRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTWT	FGQGTKVEIK
277	-	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWWT	FGQGTKVEIK
48	250	GASIRAT	GLPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNYWWT	FGQGTKVEIK
52	263	GASIRAT	GLPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNYWWT	FGQGTKVEIK
56	269	GASIRAT	GLPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNYWWT	FGQGTKVEIK

Table 33. Hybridoma Heavy Chain Analysis AB-TNFa-XG2

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	278	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
2.14	132	VH3-33/D6-19/JH6b	QVQLVESGGGVVQPGRSLRLSCAAS	GLIFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ERDSSGWYYYGMDV	WGQGTTVTVSS
2.13	128	"	QVQLVESGGGVVQPGRSLRLSCAAS	GLIFSNYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EGIAVAGPPYYYYGMDV	WGQGTTVTVSS
2.10	124	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ERDSSGWYYYGMDV	WGQGTTVTVSS
	279	**Germline**	EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSYAMS	WVRQAPGKGLEWVS	AISGSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK		WGQGTLVTVSS
4.23	262	VH3-23/D3-22/JH4b	EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSYAMS	WVRQAPGKGLEWVS	AISGSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	DYYDSSGYHPFDY	WGQGTLVTVSS
	280	**Germline**	EVQLVESGGGLVKPGGSLRLSCAAS	GFTFSSYSMN	WVRQAPGKGLEWVS	SISSSSSYIYYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCA#		WGQGTTVTVSS
2.21	158	VH3-21/D1-20/JH6b	EVQLVESGGGLVKPGGSLRLSCAAS	GFTFSSYSMN	WVRQAPGKGLEWVS	SISSSSSYIYYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	GGITGTTNYYGMDV	WGQGTTVTVSS
	281	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTLVTVSS
4.7	198	VH3-33/D6-19/JH4b	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	IIWYDGSNEYYGDSVKG	RFTISRDNSKNTLFLQMNSLRAEDTAVYYCAR	DPLRIVVAGDFDY	WGQGTLVTVSS
4.11	214	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	IIWYDGSNEYYGDSVKG	RFTISRDNSKNTLFLQMNSLRAEDTAVYYCAR	DPLRIVVAGDFDY	WGQGTLVTVSS
	282	**Germline**	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTMVTVSS
3.9	186	VH3-53/--/JH3b	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GPGAFDI	WGQGTMVTVSS
3.8	182	"	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSNNYMH	WVRQAPGKGLEWVS	VIYSGGNTYYADSVKG	RFTISRDNSKNTLFLQMNSLKTEDTAVYYCAR	GPGAFDI	WGQGTMVTVSS
	283	**Germline**	EVQLVQSGAEVKKPGESLKISCKGS	GYSFTSYWIG	WVRQMPGKGLEWMG	IIYPGDSDTRYSPSFQG	QVTISADKSISTAYLQWSSLKASDTAMYYCAR		WGQGTTVTVSS
2.4	100	VH5-51/D3-3/JH6b	EVQLVQSGAEVKKPGESLKISCKGS	GYSFTSDWIG	WVRQMPGKGLEWMG	IIYPGDSDTRYSPSFQG	QVTISADKSITTAYLQWSSLKASDTAMYYCAR	SGYGMDV	WGQGTTVTVSS
	284	**Germline**	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYGIS	WVRQAPGQGLEWMG	WISAYNGNTNYAQKLQG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR		WGQGTLVTVSS
3.4	170	VH1-18/D6-19/JH4b	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTFYSIT	WVRQAPGQGLEWMG	WISAYNDNTNYAQKLQG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	TFTSGFDY	WGQGTLVTVSS
	285	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTLVTVSS
2.3	96	VH3-33/D4-23/JH4b	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMN	WVRQAPGKGLEWVA	VIWYDGSNKYYGDSVKG	RFTISRDNSKNTLYVQMNSLRAEDTAVYYCAR	ESDYGGNPYFDY	WGQGTLVTVSS

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
4.8	202	"	QVHLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWHDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCTR	ESDYGGYPYFD Y	WGQGILATVSS
4.4	194	"	QVHLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWHDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCTR	ESDYGGYPYFD Y	WGQGILATVSS
4.3	190	"	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ESDYGGNPYFD Y	WGQGTLAAVSS
	286	Germline	EVQLVESGGGLIQPGGSLRLS CAAS	GFTVSSNYMS	WVRQAPGKGLE WVS	VIYSGGSTYYA DSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTLVTVSS
2.17	144	VH3-53/D7-27/JH4b	EVQLVESGGGLIQPGGSLRLS CAAS	GFTVSSNYVN	WVRQAPGKGLE WVS	VIYNAGSAYYA DSVKG	RFTISRDNSKNTLFLQMNSLR AEDTAVYYCAR	GTGAFDY	WGQGTLVTVSS
	287	Germline	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VISYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
4.13	222	VH3-30/D4-17/JH6b	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYDMH	WVRQAPGKGLE WVA	IISYDGSIKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ENAVTYGGYYH YGMDV	WGQGTTVTVSS
	288	Germline	QVQLVESGGGLVKPGGSLRLS CAAS	GFTFSDYYMS	WIRQAPGKGLE WVS	YISSSGSTIYY ADSVKG	RFTISRDNAKNSLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
1.1	84	VH3-11/--/JH6b	QVQLVESGGGLVKPGGSLRLS CAAS	GFTFSDYYMS	WIRQAPGKGLE WVS	YISRSGSTIYY ADSVKG	RFTISRDNAKNSLYLQMNSLR AEDTAVYYCAR	SLGGMDV	WGQGTTVTVSS
2.16	140	"	QVQLVESGGGLVKPGGSLRLS CAAS	GFTFSDYYMS	WIRQAPGKGLE WVS	YISRSGSTIYY ADSVKG	RFTISRDNAKNSLYLQMNSLR AEDTAVYYCAR	SLGGMDV	WGQGTTVTVSS
2.18	148	"	QVQLVESGGGLVKPGGSLRLS CAAS	GFTFSDYYMS	WIRQAPGKGLE WVS	YISRSGSTIYY ADSVKG	RFTISRDNAKNSLYLQMNSLR AEDTAVYYCAR	SLGGMDV	WGQGTTVTVSS
	289	Germline	QVQLVESGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
4.12	218	VH3-33/D4-17/JH6b	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ETTVTKEGIYY YGMDV	WGQGTTVTVSS
4.9	206	"	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ETTVTKEGIYY YGMDV	WGQGTTVTVSS
	290	Germline	QVQLVQSGAEVKKPGASVKVS CKAS	GYTFTSYGIS	WVRQAPGQGLE WMG	WISAYNGNTNY AQKLQG	RVTMTTDTSTSTAYMELRSLR SDDTAVYYCAR		WGQGTLVTVSS
2.6	108	VH1-18/D1-7/JH4b	QVQLVQSGAEVKKPGASVKVS CKAS	GYTFTSYGIS	WVRQAPGQGLE WMG	WISAYNVNTNY AQKLQG	RVTMTTDTSTNTAYMELRSLR SDDTAVYYCAR	DPITETMEDYF DY	WGQGTLVTVSS
	291	Germline	EVQLVQSGAEVKKPGESLKIS CKGS	GYSFTSYWIG	WVRQMPGKGLE WMG	IIYPGDSDTRY SPSFQG	QVTISADKSISTAYLQWSSLK ASDTAMYYCAR		WGQGTLVTVSS
3.2	166	VH5-51/D7-27/JH4b	EVQLVQSGAEVKKPGESLKIS CKTS	GYSFTSYWIG	WVRQMPGKGLE WMG	IIYLGDSDTRY SPSFQG	QVTISADKSISTAYLQWSSLK ASDTAMYYCAR	SNWGLDY	WGQGTLVTVSS
	292	Germline	QVQLVESGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
4.16	234	VH3-33/D2-21/JH6b	QVQLVESGGVVQPGRSLRLS CTTS	GFTFSNYGMH	WVRQAPGKGLE WVA	VIWYDGSIKYY VDSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	EKDCGGDCYSH YGMDV	WGQGTTVTVSS
4.15	230	"	QVQLVESGGGVVQPGRSLRLS CTTS	GFTFSNYGMH	WVRQAPGKGLE WVA	VIWYDGSIKYY VDSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	EKDCGGDCYSH YGMDV	WGQGTTVTVSS
4.14	226	"	QVQLVESGGGVVQPGRSLRLS CTTS	GFTFSNYGMH	WVRQAPGKGLE WVA	VIWYDGSIKYY VDSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	EKDCGGDCYSH YGMDV	WGQGTTVTVSS

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
4.17	238	"	QVQLVESGGGVVQPGRSLRLSCTTS	GFTFSNYGMH	WVRQAPGKGLEWVA	VIWYDGSIKYYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EKDCGGDCYSHYGMDV	WGQGTTVTVSS
	293	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
2.1	88	VH3-33/--/JH6b	QVQLVESGGDVVQPGRSLRLSCAAS	GFTFSSSGMH	WVRQAPGKGLEWVA	IIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDYYYGMDV	WGQGTTVTVSS
	294	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTLVTVSS
2.2	92	VH3-33/D4-23/JH4a	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGNNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ESDYGGNPYFDY	WGQGTTVTVSS
	295	**Germline**	QVQLQESGPGLVKPSETLSLTCTVS	GGSISSYYWS	WIRQPPGKGLEWIG	YIYYSGSTNYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR		WGQGTLVTVSS
3.6	178	VH4-59/D6-19/JH4b	QVQLQESGPGLVKPSETLSLTCTVS	GGSISSYYWS	WIRQPPGKGLEWIG	YFYYSGSTNYNPSLKS	RVTISVDTSKNQFSLKLRSVTAADTAVYYCAR	DRFTSGWFDY	WGQGTLVTVSS
	296	**Germline**	EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSSYSMN	WVRQAPGKGLEWVS	YISSSSSTIYYADSVKG	RFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR		WGQGTLVTVSS
4.22	258	VH3-48/D1-14/JH4b	EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSNYGMN	WVRQAPGKGLEWVS	YISNSITSKYYADSVKG	RFTISRDNAKNSLYLQMNSLRDVDTAVYHCAR	GPGGFDY	WGQGTLVTVSS
	297	**Germline**	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTLVTVSS
2.9	120	VH3-53/--/JH4b	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGGTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GPGSFDY	WGQGTLVTVSS
	298	**Germline**	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTGYYMH	WVRQAPGQGLEWMG	WINPNSGGTNYAQKFQG	RVTMTRDTSISTAYMELSRLRSDDTAVYYCAR		WGQGTTVTVSS
3.1	162	VH1-2/D6-19/JH6b	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTGYYMH	WVRQAPGQGLEWMG	WINPNSGGTNYAQKFQG	RVTMTRDTSISTAYMELSRLRSDDTAVYYCAR	APLWTVRSWYYYGMDV	WGQGTTVTVSS
	299	**Germline**	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
4.19	246	VH3-33/D3-9/JH6b	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGRNKYNADSVKG	RFTISRDNSKNTLNLQMNSLRAEDTAVYYCAR	DLTYYDILGGMDV	WGQGTTVTVSS
4.18	242	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGRNKYNADSVKG	RFTISRDNSKNTLNLQMNSLRAEDTAVYYCAR	DLTYYDILGGMDV	WGQGTTVTVSS
2.8	116	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGRNKYNADSVKG	RFTISRDNSKNTLNLQMNSLRAEDTAVYYCAR	DLTYYDILGGMDV	WGQGTTVTVSS
4.20	250	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGRNKYNADSVKG	RFTISRDNSKNTLNLQMNSLRAEDTAVYYCAR	DLTYYDILGGMDV	WGQGTTVTVSS
2.7	112	"	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA	VIWYDGRNKYNADSVKG	RFTISRDNSKNTLNLQMNSLRAEDTAVYYCAR	DLTYYDILGGMDV	WGQGTTVTVSS
	300	**Germline**	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR		WGQGTTVTVSS
2.19	152	VH3-53/--/JH6b	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GEGGMDV	WGQGTTVTVSS
2.15	136	"	EVQLVESGGGLIQPGGSLRLSCAAS	GFTVSSNYMS	WVRQAPGKGLEWVS	VIYSGGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GEGGMDV	WGQGTTVTVSS

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	301	**Germline**	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
2.5	104	VH3-33/D3-10/JH6b	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYDMH	WVRQAPGKGLE WVA	VIWYDGSNKYH ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ENTMVRGGDYY YGMDV	WGQGTTVTVSS
3.5	174	"	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYDMH	WVRQAPGKGLE WVA	VIWYDGSNKYH ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	ENTMVRGGDYY YGMDV	WGQGTTVTVSS
	302	**Germline**	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTLVTVSS
4.10	210	VH3-33/D4-17/JH5b	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	SRYGDWGWFDP	WGQGTLVTVSS
	303	**Germline**	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR		WGQGTTVTVSS
4.21	254	VH3-33/D6-19-D7-27/JH6b	QVQLVESGGGVVQPGRSLRLS CAAS	GFTFSSYGMH	WVRQAPGKGLE WVA	VIWYDGSNKYY ADSVKG	RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR	GNRVVVAGTRV TPANWGIYYYG MDV	WGQGTTVTVSS

Table 34. Hybridoma Light Chain Analysis AB-TNFa-XG2K

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	304	**Germline**	QSVLTQPPSVSGAPGQRVTISC	TGSSSNIGAGYDVH	WYQQLPGTAPKLLIY	GNSNRPS	GVPDRFSGSKSGTSASLAITGLQAEDEADYYC	QSYDSSLSGSV	FGGGTKLTVL
2.4	102	V1-13/JL2	QSLLTQPPSVSGAPGQRVTISC	TGSSSNIGAGYDVH	WYQQFPGTAPKLLIY	GNSNRPS	GVPDRFSGSKSGTSASLAITGLQAEDEADYYC	QSYDSSLSGSV	FGGGTKLTVL
4.7	200	"	QSVLTQPPSVSGAPGLRVTISC	TGNSSNIGAGYDVH	WYQQLPGTAPKLLIY	GNSNRPS	GVPDRFSGSKSGTSASLAITGLQAEDETDYYC	QSYDSSLSGSV	FGGGTKLTVL
	305	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4.9	208	A30/JK4	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4.21	256	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKCLIY	VASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4.20	252	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRHDLG	WYQQKPGKAPERLIY	GASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4.17	240	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHMSLPLT	FGGGTKVEIK
4.16	236	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHMSLPLT	FGGGTKVEIK
2.14	134	"	DIQMTQSPSSLSASVGDRVTITC	RASQAIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSRSGTEFTLTISSLQPEDFASYYC	LQHRSYPLT	FGGGTKVEIK
4.15	232	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHMSLPLT	FGGGTKVEIK
3.9	188	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WFQQKPGKAPKRLIY	AASNFLS	GVPSRFSGSGSGTEFTLTISSLQPEDFTTYYC	LQHNPYPPRLT	FGGGTKVEIK
4.14	228	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHMSLPLT	FGGGTKVEIK
4.13	224	"	DIQMTQSPSSLSTSVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
4.12	220	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
2.10	126	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTVSSLQPEDFATYYC	LQHNSLPLT	FGGGTKVEIK
3.6	180	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPRKAPKRLIF	AASSLQS	GVPSRFSGSGSGPEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK
3.5	176	"	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPRKAPKRLIF	AASSLQS	GVPSRFSGSGSGPEFTLTISSLQPEDFATYYC	LQHNSYPLT	FGGGTKVEIK

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	306	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WYQQKPGKVPKLLIY	AASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	QKYNSAPFT	FGPGTKVDIK
4.23	264	A20/JK3	DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WYQQKPGKVPKFLIY	AASTLQS	GVPSRFSGSGSGTDFTLTVSSLQPEDVATYYC	QMYNSVPFT	FGPGTKVDIK
	307	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPWT	FGQGTKVEIK
4.22	260	A30/JK1	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKCLIY	VASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPWT	FGQGTKVEIK
	308	**Germline**	DIQMTQSPSSLSASVGDRVTITC	RASQSISSYLN	WYQQKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSTPIT	FGQGTRLEIK
2.16	142	O12/JK5	DIQMTQSPSSLSASVGDRVAITC	RTSQSISSYLN	WYQQKPGKAPELLIY	AASNLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSSSTLIT	FGQGTRLEIK
2.19	156	"	DIQMTQSPSSLSASVGDRVTITC	RTSQSISSYLN	WYQQKPGKAPEVLIY	AASNLQR	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSSSTLIT	FGQGTRLEIK
2.18	150	"	DIQMTQSPSSLSASVGDRVTITC	RTSQSISSYLN	WYHQKPGKAPELLIY	AAFNLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSSSTLIT	FGQGTRLEIK
2.21	160	"	DIQMTQSPSSLSASVGDRVTITC	RTSQSISSYLN	WYQQKPGKAPELLIY	AAFNLQS	GVPSRISGSGSGTDFTLTISSLHPEDFATYYC	QQSSSTLIT	FGQGTRLEIK
	309	**Germline**	QSVLTQPPSVSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQLPGTAPKLLIY	DNNKRPS	GIPDRFSGSKSGTSATLGITGLQTGDEADYYC	GTWDSSLSAGV	FGGGTKLTVL
3.1	164	V1-19/JL3	QSVLTQPPSMSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQLPGIAPKLLIY	DNNKRPS	GIPDRFSGSKSGTSATLGITGLQTGDEADYYC	GTWDSSLSAGV	FGGGTKLTVL
1.1	86	"	QSVLTQPPSVSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQFPGTAPKLLIY	DNNSRPS	GIPDRFSGSKSGTSATLGITGLQTGDEADYYC	GTWDSSLSAGV	FGGGTKLTVL
	310	**Germline**	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWPIT	FGQGTRLEIK
3.8	184	L2/JK5	EIVMTQSPATLSVSPGERVTLSC	RASQSATSNLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWPFT	FGQGTRLEIK
	311	**Germline**	QSVLTQPPSVSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQLPGTAPKLLIY	DNNKRPS	GIPDRFSGSKSGTSATLGITGLQTGDEADYYC	GTWDSSLSAGV	FGGGTKLTVL
2.1	90	V1-19/JL2	QSALTQPPSVSAAPGQKVTISC	SGSSSNIGSNYVS	WCQQLPRTAPKLLIY	DNNKRPS	GIPDRFSGSKSGTSATLVITGLQTGDEADYYC	GAWDSSLSAGV	FGGGTKLTVL
	312	**Germline**	DIQMTQSPSSVSASVGDRVTITC	RASQGISSWLA	WYQQKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPWT	FGQGTKVEIK
2.9	122	L5/JK1	DIQMTQSPSSVSASVGDRVTITC	RASQGISSWLA	WYQQKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFASYYC	QQANSFPWT	FGQGTKVEIK
	313	**Germline**	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWPLT	FGGGTKVEIK
4.11	216	L2/JK4	EIVMTQSPATLSVSPGERATLSC	RASQSVISNLA	WYQQPGQAPRLLIY	GASTRAT	GFPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWPLT	FGGGTKVEIK
2.17	146	"	EIVMTQSPATLSVSPGERATLSC	RASQSVSSNLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSRTGTEFTLTISSLQSEDFAVYYC	QQYNNWPLT	FGGGTKVEIK

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	314	Germline	EIVMTQSPATLSVSPGERATL SC	RASQSVSSNLA	WYQQKPGQAPR LLIY	GASTRAT	GIPARFSGSGSGTEFTLTISS LQSEDFAVYYC	QQYNNWPFT	FGPGTKVDIK
4.18	244	L2/JK3	EIVMTQSPATLSVSPGERATL SC	RASQSVTSNLA	WYQQKPGQAPR LLIY	GASTRAT	GIPARFSGSGSGTEFTLTISS LPSEDFAVYYC	QQYHTWPFT	FGPGTKVDIK
2.15	138	"	EIVMTQSPSTLSVSPGERATL SC	RASQSVSSNLA	WYQQKPGQAPR LLIY	GASIRAT	GIPARFSGSGSGTEYTLTISS LQSEDFAVYYC	QQYNNWPFT	FGPGTKVDIK
4.19	248	"	EIVMTQSPSTLSVSPGERATL SC	RASQSVTSNLA	WYQQKPGQAPR LLIY	GASTRAT	GIPARFSGSGSGTEFTLTISS LPSEDFAVYYC	QQYHTWPFT	FGPGTKVDIK
	315	Germline	QSVLTQPPSASGTPGQRVTIS C	SGSSSNIGSNT VN	WYQQLPGTAPK LLIY	SNNQRPS	GVPDRFSGSKSGTSASLAISG LQSEDEADYYC	AAWDDSLNGPV	FGGGTKLTVL
4.10	212	V1-16/JL3	QSVLTQPPSASGTPGQRVTIS C	SGSSSNIGSNT VN	WYQQLPGTAPK LLIY	SNNQRPS	GVPDRFSGSKSGTSASLAISG LQSEDEADYYC	AAWDDSLNGPV	FGGGTKLTVL
	316	Germline	SSELTQDPAVSVALGQTVRIT C	QGDSLRSYYAS	WYQQKPGQAPV LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	NSRDSSGNHLV	FGGGTKLTVL
2.5	106	V2-13/JL3	SSELTQDPAVSVALGQTVRIT C	QGDSLRRYYAS	WYQQKPGQAPI LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	NSRDSSGNHLV	FGGGTKLTVL
3.4	172	"	SSELTQDPAVSVALGQTVRIT C	QGDSLRRYYAS	WYQQKPGQAPI LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	NSRDSSGNHLV	FGGGTKLTVL
	317	Germline	SYELTQPPSVSVSPGQTARIT C	SGDALPKKYAY	WYQQKSGQAPV LVIY	EDSKRPS	GIPERFSGSSSGTMATLTISG AQVEDEADYYC	YSTDSSGNHVV	FGGGTKLTVL
2.19	154	V2-7/JL2	SYELTQPPSVSVSPGQTARIT C	SGDALPKKYVY	WYQQKSGQAPV LVIY	EDSKRPS	GIPERFSGSSSGTMATLTING AQVEDEADYYC	YSTDSSGNHVV	FGGGTKLTVL
	318	Germline	DIQMTQSPSSLSASVGDRVTI TC	QASQDISNYLN	WYQQKPGKAPK LLIY	DASNLET	GVPSRFSGSGSGTDFTFTISS LQPEDIATYYC	QQYDNLPIT	FGQGTRLEIK
2.13	130	018/JK5	DIQMTQSPSSLSASVGDRVTI TC	QASQDISNYLN	WYQQKPGKAPK LLIY	DASNLET	GVPSRFSGSGSGTDFTFTISS LQPEDIATYYC	HQCDNLPH	FGQGTRLEIK
	319	Germline	SSELTQDPAVSVALGQTVRIT C	QGDSLRSYYAS	WYQQKPGQAPV LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	NSRDSSGNHVV	FGGGTKLTVL
2.3	98	V2-13/JL2	SSELTQDPAVSVALGQTVRIT C	QGDSLRIYYAS	WYQQKPGQAPV LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTVTG AQAEDEADYYC	KSRDSSFNHVT	FGGGTKLTVL
2.6	110	"	SSELTQDPAVSVALGQTVRIT C	QGDSLRNYYAS	WYQQKPGQAPI LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	NSRDSSGNHVT	FGGGTKLTVL
4.3	192	"	SSELTQDPAVSVALGQTVRIT C	QGDSLRSYYAS	WYQQKPGQAPV LVIY	GKNNRPS	GIPDRFSGSSSENTASLTITG AQAEDEADYYC	KSRDSSFNHVT	FGGGTKLTVL
4.8	204	"	SSELTQDPAVSVALGQTVRIT C	QGDILRSYYAS	WYQQKPGQAPI LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	KSRDSSYNHVT	FGGGTKLTVL
2.8	118	"	SSELTQDPAVSVALGQTVRIT C	QGDSLRRYYAS	WYQQKPGQAPI VVIY	GKKNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	KSRDSSGNHVT	FGGGTKLTVL
2.2	94	"	SSELTQDPAVSVALGQTVRIT C	QGDSLRSYYAS	WYQQRPGQAPV LVIY	GRNNRPS	GIPDRFSGSSSGLTASLTVTG AQAEDEADYYC	NSRDSSYNHVA	FGGGTKLTVL
4.4	196	"	SSELTQDPAVSVALGQTVRIT C	QGDILRSYYAS	WYQQKPGQAPV LVIY	GKNNRPS	GIPDRFSGSSSGNTASLTITG AQAEDEADYYC	KSRDSSYNHVT	FGGGTKLTVL

CHAIN NAME	SEQ ID NO:		FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
	320	**Germline**	QSVLTQPPSVSGAPGQRVTIS C	TGSSSNIGAGY DVH	WYQQLPGTAPK LLIY	GNSNRPS	GVPDRFSGSKSGTSASLAITG LQAEDEADYYC	QSYDSSLSGSV	FGGGTKLTVL
3.2	168	V1-13/JL3	QSVLTQPPSVSGAPGQRVTIS C	TGSSSNIGAGY DVH	WYQQFPGTAPK LLIQ	GNSNRPS	GVPDRFSGSKSGTSASLAITG LQAEDEADYYC	QSYDSSLSGSV	FGGGTKLTVL
2.7	114	"	QSVLTQSPSVSGAPGQRVTIS C	TGSSSNIGAGY DVH	WYQQLPGTAPR LLIY	GNNNRPS	GVPDRFSGSKSGTSASLAITG LQAEDEADYYC	QSYDSSLSGSV	FGGGTKLTVL

EXAMPLE 11

DETERMINATION OF CANONICAL CLASSES OF ANTIBODIES

[0236] Chothia, et al have described antibody structure in terms of "canonical classes" for the hypervariable regions of each immunoglobulin chain (J Mol Biol. 1987 Aug 20;196(4):901-17). The atomic structures of the Fab and VL fragments of a variety of immunoglobulins were analyzed to determine the relationship between their amino acid sequences and the three-dimensional structures of their antigen binding sites. Chothia, et al. found that there were relatively few residues that, through their packing, hydrogen bonding or the ability to assume unusual phi, psi or omega conformations, were primarily responsible for the main-chain conformations of the hypervariable regions. These residues were found to occur at sites within the hypervariable regions and in the conserved beta-sheet framework. By examining sequences of immunoglobulins having unknown structure, Chothia, et al show that many immunoglobuins have hypervariable regions that are similar in size to one of the known structures and additionally contained identical residues at the sites responsible for the observed conformation.

[0237] Their discovery implied that these hypervariable regions have conformations close to those in the known structures. For five of the hypervariable regions, the repertoire of conformations appeared to be limited to a relatively small number of discrete structural classes. These commonly occurring main-chain conformations of the hypervariable regions were termed "canonical structures". Further work by Chothia, et al. (Nature. 1989 Dec 21-28;342(6252):877-83) and others (Martin, et al. J Mol Biol. 1996 Nov 15;263(5):800-15) confirmed that that there is a small repertoire of main-chain conformations for at least five of the six hypervariable regions of antibodies.

[0238] Each of the antibodies described above was analyzed to determine the canonical class for each of the antibody's complementarity determining regions (CDRs). As is known, canonical classes have only been assigned for CDR1 and CDR2 of the antibody heavy chain, along with CDR1, CDR2 and CDR3 of the antibody light chain. The tables below (35 and 36) summarize the results of the analysis. The Canonical Class data is in the form of *HCDR1-HCDR2-LCDR1-LCDR2-LCDR3, wherein "HCDR" refers to the heavy chain CDR and "LCDR" refers to the light chain CDR. Thus, for example, a canonical class of 1-3-2-1-5 refers to an antibody that has a HCDR1 that falls into canonical class 1, a HCDR2 that falls into canonical class 3, a LCDR1 that falls into canonical class 2, a LCDR2 that falls into canonical class 1, and a LCDR3 that falls into canonical class 5.

[0239] Assignments were made to a particular canonical class where there was 70% or greater identity of the amino acids in the antibody with the amino acids defined for each canonical class. Where there was less than 70% identity, the canonical class assignment is marked with an

asterisk ("*") to indicate that the best estimate of the proper canonical class was made, based on the length of each CDR and the totality of the data. The amino acids defined for each antibody can be found, for example, in the articles by Chothia, et al. referred to above.

Table 35

Antibody	Canonical Class
3.6	1-1*-2-1-1
2.19	1-1-2*-1-5
3.9	1-1-2-1-*
2.15	1-1-2-1-1
2.17	1-1-2-1-1
2.9	1-1-2-1-1
3.8	1-1-2-1-1
250	1-1-2-1-3
263	1-1-2-1-3
269	1-1-2-1-3
69	1-1*-4-1-1
3.4	1-3*-1*-1-5*
2.6	1-3*-2*-1-5*
4.22	1-3*-2-1-1
2.4	1-3*-6-1-5
3.2	1-3*-6-1-5
2.2	1-3-2*-1-5*
2.3	1-3-2*-1-5*
2.5	1-3-2*-1-5*
2.8	1-3-2*-1-5*
4.3	1-3-2*-1-5*
4.4	1-3-2*-1-5*
4.8	1-3-2*-1-5*
15	1-3-2-1-1
28	1-3-2-1-1
95	1-3-2-1-1
148	1-3-2-1-1
2.10	1-3-2-1-1
2.13	1-3-2-1-1
2.14	1-3-2-1-1
2.16	1-3-2-1-1
2.18	1-3-2-1-1
2.21	1-3-2-1-1
234	1-3-2-1-1
280	1-3-2-1-1
282	1-3-2-1-1
291	1-3-2-1-1
299v1	1-3-2-1-1
299v2	1-3-2-1-1
3.5	1-3-2-1-1
313	1-3-2-1-1

Antibody	Canonical Class
4.11	1-3-2-1-1
4.12	1-3-2-1-1
4.13	1-3-2-1-1
4.14	1-3-2-1-1
4.15	1-3-2-1-1
4.16	1-3-2-1-1
4.17	1-3-2-1-1
4.18	1-3-2-1-1
4.19	1-3-2-1-1
4.20	1-3-2-1-1
4.21	1-3-2-1-1
4.23	1-3-2-1-1
4.9	1-3-2-1-1
140	1-3-4-1-*
1.1	1-3-5-1-5
2.1	1-3-5-1-5
3.1	1-3-5-1-5
4.10	1-3-5-1-5
2.7	1-3-6-1-5
4.7	1-3-6-1-5
2	3-1-2-1-1
25	3-1-2-1-1
123	3-1-2-1-1
131	3-1-2-1-1

EXAMPLE 12

DOMAIN ANALYSIS OF ANTI-TNF-a ANTIBODIES THROUGH EXPRESSION AND BINDING ASSAYS TO TNF-a EPITOPES

Sequencing/Binning results

[0240] The variable (V) regions of immunoglobulin chains are encoded by multiple germ line DNA segments, which are joined into functional variable regions (V_HDJ_H or V_KJ_K) during B-cell ontogeny. The Molecular and genetic diversity of the antibody response to TNF-a was studied in detail. These assays revealed several points specific to anti TNF-a. Analysis of 65 individual antibodies specific to TNF-a yielded 13 germline VH genes, 54 of them from the VH3 family, with 34 of them using the VH3-33 gene segment. The most frequent gene, VH3-33 germline gene was expressed in 34 of the 65 antibodies analyzed, and was limited to 2 different bins with clear linkage to the type of the light chain involved in the binding (Kappa A30 versus L2 or lambda). Selection of functional antibodies and binning showed that antibodies in specific bin expressed the same Ig V_H and in some cases the same V_HDJ_H rearrangements. Furthermore, it was also discovered that pairs of

H and L chain were conserved within the bin. These findings suggest that, for any given epitope, only a few members of the germ line repertoire are used to form the corresponding paratope, and for each antigenic epitope a limited number of L- and H –chain genes can pair to form a specific paratope.

[0241] The location of biologically relevant epitopes on human TNF-a was evaluated by expression and binding assay of mAbs specific for human TNF-a to a set of chimeric human/mouse TNF-a molecules. The antibodies described above fall into 4 major binning groups, all linked to several sites crucial for hTNF-a biological activity. The N-terminal domain of TNF-a was found to be involved in receptor binding.

[0242] In the first group antibodies, which neutralize TNF-a activity through direct binding to TNF-a receptor binding domain, all recognized sequences in the first 36 residues of the secreted TNF-a molecule. The results showed that both receptors bind to the same N-terminal region. Van Ostade et al, ((1993) nature, 361:266-269) reported that the P75 Receptor binding domain was localized in loops at the base of the molecule, and that single amino substitutions at position 29 and 32 reduced binding activities with the p75 receptor. Antibodies in group I (VH3-33/JH6b coupled with kappa chain A30/JK4) all have canonical class 1-3-2-1-1. All tested antibodies exhibit binding to the first 36 residues, with Lys11 and Arg31 present. Antibodies expressing VH3-33/Jh6b coupled with lambda as a light chain showed different specificity.

[0243] Van Ostade et al ((1991) *EMBO* 10:827-836) demonstrated that by means of random and site directed mutagenesis, the integrity of four regions amino-acid 32-34, 84-91, 117-119 and 143-148 is important for maintaining the biological activity. Antibodies using the VH3-33/JH4b coupled with L2 kappa chain were shown to recognize different discontinuous domains of the TNF-a molecule. These antibodies were highly specific for human TNF-a, and their epitope is a constellation of residues located in different, noncontiguous positions of the TNF Polypeptide.

[0244] The third group of antibodies includes antibodies utilizing VH3-33 coupled to lambda light chain as mAb 3.2 . The binding site of this group lies between residues 1-91. Although replacement of Gln27 and arg31 did not affect the binding to human TNF-a, the N-terminus appeared important for their binding activity. The results are provided below in Table 36.

Table 36

TNF Epitope	mAb	VH	DH	JH	VK	JK	VL	JL	Canonical Class
	3.1	VH1-2	D6-19	JH6b			V1-19	JL3	1-3-5-1-5
1-91	2.6	VH1-18	D1-7	JH4b			V2-13	JL2	1-3*-2*-1-5*
1-125	3.4	VH1-18	D6-19	JH4b			V2-13	JL3	1-3*-1*-1-5*
	1.1	VH3-11	D3-16	JH6b			V1-19	JL3	1-3-5-1-5
	2.16	VH3-11	D3-16	JH6b	O12	JK5			1-3-2-1-1
	2.18	VH3-11	D3-16	JH6b	O12	JK5			1-3-2-1-1
1-125	2.21	VH3-21	D1-20	JH6b	O12	JK5			1-3-2-1-1
	4.23	VH3-23	D3-22	JH4b	A20	JK3			1-3-2-1-1
	4.13	VH3-30	D4-17	JH6b	A30	JK4			1-3-2-1-1
	SC234	VH3-30	D1-26	JH6b	A30	JK4			1-3-2-1-1
	SC140	VH3-30	D1-20	JH6b	A19	JK1			1-3-4-1-*
	SC28	VH3-30	D3-3	JH6b	A30	JK1			1-3-2-1-1
1-157	4.11	VH3-33	D6-19	JH4b	L2	JK4			1-3-2-1-1
	4.19	VH3-33	D3-9	JH6b	L2	JK3			1-3-2-1-1
1-157	4.18	VH3-33	D3-9	JH6b	L2	JK3			1-3-2-1-1
	4.7	VH3-33	D6-19	JH4b			V1-13	JL2	1-3-6-1-5

TNF Epitope	mAb	VH	DH	JH	VK	JK	VL	JL	Canonical Class
	2.8	VH3-33	D3-9	JH6b			V2-13	JL2	1-3-2*-1-5*
36-91	2.7	VH3-33	D3-9	JH6b			V1-13	JL3	1-3-6-1-5
	2.1	VH3-33		JH6			V1-19	JL2	1-3-5-1-5
	2.2	VH3-33	D4-23	JH4a			V2-13	JL2	1-3-2*-1-5*
	2.5	VH3-33	D3-10	JH6b			V2-13	JL3	1-3-2*-1-5*
	4.4	VH3-33	D4-23	JH4b			V2-13	JL2	1-3-2*-1-5*
1-157	4.3	VH3-33	D4-23	JH4b			V2-13	JL2	1-3-2*-1-5*
	4.10	VH3-33	D4-17	JH5b			V1-16	JL3	1-3-5-1-5
	2.3	VH3-33	D4-23	JH4b			V2-13	JL2	1-3-2*-1-5*
	4.8	VH3-33	D4-23	JH4b			V2-13	JL2	1-3-2*-1-5*
	2.13	VH3-33	D6-19	JH6b	O18	JK5			1-3-2-1-1
	4.20	VH3-33	D3-9	JH6b	A30	JK4			1-3-2-1-1
	4.21	VH3-33		JH6b	A30	JK4			1-3-2-1-1
	2.14	VH3-33	D6-19	JH6b	A30	JK4			1-3-2-1-1
1-36	2.10	VH3-33	D6-19	JH6b	A30	JK4			1-3-2-1-1
	3.5	VH3-33	D3-10	JH6b	A30	JK4			1-3-2-1-1
	4.12	VH3-33	D4-17	JH6b	A30	JK4			1-3-2-1-1

TNF Epitope	mAb	VH	DH	JH	VK	JK	VL	JL	Canonical Class
	4.9	VH3-33	D4-17	JH6b	A30	JK4			1-3-2-1-1
	SC280	VH3-33	D4-17	JH6b	A30	JK1			1-3-2-1-1
	SC282	VH3-33	D4-17	JH6b	A30	JK1			1-3-2-1-1
	SC291	VH3-33	D1-26	JH6b	A30	JK4			1-3-2-1-1
	4.16	VH3-33	D2-21	JH6b	A30	JK4			1-3-2-1-1
1-36	4.17	VH3-33	D2-21	JH6b	A30	JK4			1-3-2-1-1
	4.14	VH3-33	D2-21	JH6b	A30	JK4			1-3-2-1-1
	4.15	VH3-33	D2-21	JH6b	A30	JK4			1-3-2-1-1
1-36	SC299	VH3-33	D5-5	JH6b	A30	JK4			1-3-2-1-1
	SC313	VH3-33	D5-24	JH6b	A30	JK4			1-3-2-1-1
	SC148	VH3-33	D5-5	JH6b	A30	JK4			1-3-2-1-1
	SC15	VH3-33	D6-6	JH6b	A30	JK4			1-3-2-1-1
	SC95	VH3-33	D6-19	JH6b	A30	JK4			1-3-2-1-1
	4.22	VH3-48	D1-14	JH4b	A30	JK1			1-3*-2-1-1
	3.7	VH3-53	D3-1	JH3	L2	JK4			
	2.17	VH3-53	D7-27	JH4b	L2	JK4			1-1-2-1-1
1-157	2.9	VH3-53	D7-27	JH4b	L5	JK1			1-1-2-1-1
1-125	2.19	VH3-53	D1-1	JH6	O12	JK5			1-1-2*-1-5
	2.15	VH3-53	D1-1	JH6	L2	JK3	V2-7	JL2	1-1-2-1-1
	3.8	VH3-53	D1-14	JH3b	L2	JK5			1-1-2-1-1

TNF Epitope	mAb	VH	DH	JH	VK	JK	VL	JL	Canonical Class
1-157	3.9	VH3-53	D1-14	JH3b	A30	JK4			1-1-2-1-*
	SC250	VH3-53	D3-16	JH4b	L2	JK1			1-1-2-1-3
1-157	SC263	VH3-53	D3-16	JH4b	L2	JK1			1-1-2-1-3
	SC269	VH3-53	D3-16	JH4b	L2	JK1			1-1-2-1-3
	SC69	VH4-4	D2-2	JH2	A1	JK4			1-1*-4-1-1
	SC2	VH4-31	D1-20	JH6b	A30	JK4			3-1-2-1-1
	SC25	VH4-31	D1-20	JH6b	A30	JK4			3-1-2-1-1
	SC131	VH4-31	D1-20	JH6b	A30	JK4			3-1-2-1-1
	SC123	VH4-31	D1-20	JH6b	A30	JK4			3-1-2-1-1
1-157	3.6	VH4-59	D6-19	JH4b	A30	JK4			1-1*-2-1-1
1-91	3.2	VH5-51	D7-27	JH4b			V1-13	JL3	1-3*-6-1-5
36-91	2.4	VH5-51	D3-3	JH6b			V1-13	JL2	1-3*-6-1-5

EXAMPLE 13

USES OF ANTI-TNFa ANTIBODIES AND ANTIBODY CONJUGATES FOR ARTHRITIS TREATMENT

[0245] To determine the *in vivo* effects of anti-TNFa antibody treatment in human patients with arthritis, such human patients are injected over a certain amount of time with an effective amount of anti-TNFa antibody. At periodic times during the treatment, the human patients are monitored to determine whether their arthritis is being treated.

[0246] An arthritic patient treated with anti-TNFa antibodies has a lower level of arthritic symptoms, including inflammation, as compared to arthritic patients treated with control antibodies. Control antibodies that may be used include antibodies of the same isotype as the anti-TNFa antibodies tested and further, may not have the ability to bind to TNFa antigen.

EXAMPLE 14

USE OF ANTI-TNFa ANTIBODIES AS A DIAGNOSTIC AGENT

Detection of TNFa antigen in a sample

[0247] An Enzyme-Linked Immunosorbent Assay (ELISA) for the detection of TNFa antigen in a sample may be developed. In the assay, wells of a microtiter plate, such as a 96-well microtiter plate or a 384-well microtiter plate, are adsorbed for several hours with a first fully human monoclonal antibody directed against the antigen. The immobilized antibody serves as a capture antibody for any of the antigen that may be present in a test sample. The wells are rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

[0248] Subsequently the wells are treated with a test sample suspected of containing the antigen, or with a solution containing a standard amount of the antigen. Such a sample may be, for example, a serum sample from a subject suspected of having levels of circulating antigen considered to be diagnostic of a pathology.

[0249] After rinsing away the test sample or standard, the wells are treated with a second fully human monoclonal anti-TNFa antibody that is labeled by conjugation with biotin. The labeled anti-TNFa antibody serves as a detecting antibody. After rinsing away excess second antibody, the wells are treated with avidin-conjugated horseradish peroxidase (HRP) and a suitable chromogenic substrate. The concentration of the antigen in the test samples is determined by comparison with a standard curve developed from the standard samples.

[0250] This ELISA assay provides a highly specific and very sensitive assay for the detection of the TNFa antigen in a test sample.

Determination of TNFa antigen concentration in patients

[0251] A sandwich ELISA is developed to quantify TNFa levels in human serum. The 2 fully human monoclonal anti-TNFa antibodies from the sandwich ELISA, recognizes different epitopes on the TNFa molecule. The ELISA is performed as follows: 50μL of capture anti-TNFa antibody in coating buffer (0.1 M $NaHCO_3$, pH 9.6) at a concentration of 2μg/mL is coated on ELISA plates (Fisher). After incubation at 4°C overnight, the plates are treated with 200μL of blocking buffer (0.5% BSA, 0.1% Tween 20, 0.01% Thimerosal in PBS) for 1 hour at 25°C. The plates are washed (3x) using 0.05% Tween 20 in PBS (washing buffer, WB). Normal or patient sera (Clinomics, Bioreclaimation) are diluted in blocking buffer containing 50% human serum. The plates are incubated with serum samples overnight at 4°C, washed with WB, and then incubated with

100μL/well of biotinylated detection anti-TNFa antibody for 1 hour at 25°C. After washing, the plates are incubated with HRP-Streptavidin for 15 min, washed as before, and then treated with 100μL/well of o-phenylenediamine in H_2O_2 (Sigma developing solution) for color generation. The reaction is stopped with 50μL/well of H_2SO_4 (2M) and analyzed using an ELISA plate reader at 492 nm. Concentration of TNFa antigen in serum samples is calculated by comparison to dilutions of purified TNFa antigen using a four parameter curve fitting program.

EQUIVALENTS

[0252] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and Examples detail certain preferred embodiments of the invention and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

WHAT IS CLAIMED IS:

1. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Ser Tyr Asp Met His".

2. The human monoclonal antibody of Claim 1, comprising a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly".

3. The human monoclonal antibody of Claim 2, comprising a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val".

4. The human monoclonal antibody of Claim 1, comprising a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 70.

5. The human monoclonal antibody of Claim 1, comprising a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 74.

6. The human monoclonal antibody of Claim 1, comprising a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly".

7. The human monoclonal antibody of Claim 6, comprising a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Ala Ala Ser Thr Leu Gln Ser".

8. The human monoclonal antibody of Claim 7, comprising a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Leu Gln His Lys Ser Tyr Pro Leu Thr".

9. The human monoclonal antibody of Claim 6, comprising a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 72.

10. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly".

11. The human monoclonal antibody of Claim 10, comprising a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Ala Ala Ser Thr Leu Gln Ser".

12. The human monoclonal antibody of Claim 11, comprising a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Leu Gln His Lys Ser Tyr Pro Leu Thr".

13. The human monoclonal antibody of Claim 10, comprising a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Ser Tyr Asp Met His".

14. The human monoclonal antibody of Claim 13, comprising a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly".

15. The human monoclonal antibody of Claim 14, comprising a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val".

16. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises VH3-33 heavy chain gene, or conservative variant thereof.

17. The human monoclonal antibody of Claim 16, comprising an A30VK1 light chain gene.

18. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a, wherein antibody comprises a heavy chain complementarity determining region 1 (CDR1) corresponding to canonical class 1.

19. The human monoclonal antibody of Claim 18, wherein said antibody comprises a heavy chain complementarity determining region 2 (CDR2) corresponding to canonical class 3.

20. The human monoclonal antibody of Claim 19, wherein said antibody comprises a light chain complementarity determining region 1 (CDR1) corresponding to canonical class 2.

21. The human monoclonal antibody of Claim 20, wherein said antibody comprises a light chain complementarity determining region 2 (CDR2) corresponding to canonical class 1.

22. The human monoclonal antibody of Claim 21, wherein said antibody comprises a light chain complementarity determining region 3 (CDR3) corresponding to canonical class 1.

23. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Asn Tyr Met Ser".

24. The human monoclonal antibody of Claim 23, comprising a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly".

25. The human monoclonal antibody of Claim 24, comprising a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gly Glu Gly Gly Phe Asp Tyr".

26. The human monoclonal antibody of Claim 23, comprising a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 50.

27. The human monoclonal antibody of Claim 23, comprising a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala".

28. The human monoclonal antibody of Claim 27, comprising a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Gly Ala Ser Ile Arg Ala Thr".

29. The human monoclonal antibody of Claim 28, comprising a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gln Gln Tyr Asn Tyr Trp Trp Thr".

30. The human monoclonal antibody of Claim 23, comprising a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 52.

31. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala".

32. The human monoclonal antibody of Claim 31, comprising a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Gly Ala Ser Ile Arg Ala Thr".

33. The human monoclonal antibody of Claim 32, comprising a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gln Gln Tyr Asn Tyr Trp Trp Thr".

34. The human monoclonal antibody of Claim 31, comprising a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of "Arg Asn Tyr Met Ser".

35. The human monoclonal antibody of Claim 34, comprising a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of "Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly".

36. The human monoclonal antibody of Claim 35, comprising a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of "Gly Glu Gly Gly Phe Asp Tyr".

37. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a and comprises VH3-53 heavy chain gene, or conservative variant thereof.

38. The human monoclonal antibody of Claim 37, comprising an L2VK3 light chain gene.

39. A human monoclonal antibody that specifically binds to Tumor Necrosis Factor-a, wherein antibody comprises a heavy chain complementarity determining region 1 (CDR1) corresponding to canonical class 1.

40. The human monoclonal antibody of Claim 39, wherein said antibody comprises a heavy chain complementarity determining region 2 (CDR2) corresponding to canonical class 1.

41. The human monoclonal antibody of Claim 40, wherein said antibody comprises a light chain complementarity determining region 1 (CDR1) corresponding to canonical class 2.

42. The human monoclonal antibody of Claim 41, wherein said antibody comprises a light chain complementarity determining region 2 (CDR2) corresponding to canonical class 1.

43. The human monoclonal antibody of Claim 42, wherein said antibody comprises a light chain complementarity determining region 3 (CDR3) corresponding to canonical class 3.

44. A method for assaying the level of tumor necrosis factor alpha (TNFa) in a patient sample, comprising contacting an anti-TNFa antibody of Claim 1 or Claim 23 with a biological sample from a patient, and detecting the level of binding between said antibody and TNFa in said sample.

45. The method according to Claim 44 wherein the biological sample is blood.

46. A composition, comprising an antibody of Claim 1 or Claim 23, or functional fragment thereof, and a pharmaceutically acceptable carrier.

47. A method of effectively treating an animal suffering from a neoplastic disease, comprising:

selecting an animal in need of treatment for a neoplastic disease; and

administering to said animal a therapeutically effective dose of a fully human monoclonal antibody of Claim 1 or Claim 23 that specifically binds to tumor necrosis factor alpha (TNFa).

48. The method of claim 47, wherein said neoplastic disease is selected from the group consisting of: breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, stomach cancer, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and prostrate cancer.

49. A method of effectively treating an immuno-mediated inflammatory disease, comprising:

selecting an animal in need of treatment for an inflammatory condition; and

administering to said animal a therapeutically effective dose of a fully human monoclonal antibody of Claim 1 or Claim 23, wherein said antibody specifically binds to tumor necrosis factor alpha (TNFa).

50. The method of claim 49, wherein said immuno-mediated inflammatory disease is selected from the group consisting of: rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, ankylosing spondylitis and multiple sclerosis.

51. A method of inhibiting tumor necrosis factor alpha (TNFa) induced apoptosis in an animal, comprising:

selecting an animal in need of treatment for TNFa induced apoptosis; and

administering to said animal a therapeutically effective dose of a fully human monoclonal antibody of Claim 1 or Claim 23, wherein said antibody specifically binds to TNFa.

52. Use of an antibody of Claim 1 or Claim 23 in the preparation of medicament for the treatment of neoplastic disease in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa).

53. The use of claim 52, wherein said neoplastic disease is selected from the group consisting of: breast cancer, ovarian cancer, bladder cancer, lung cancer, glioblastoma, stomach cancer, endometrial cancer, kidney cancer, colon cancer, pancreatic cancer, and prostrate cancer.

54. Use of an antibody of Claim 1 or Claim 23 in the preparation of medicament for the effective treatment of immuno-mediated inflammatory diseases in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa).

55. The use of Claim 54, wherein said immuno-mediated inflammatory disease is selected from the group consisting of: rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia, and multiple sclerosis.

56. Use of an antibody of Claim 1 or Claim 23 in the preparation of medicament for the effective treatment of tumor necrosis factor induced apoptosis in an animal, wherein said monoclonal antibody specifically binds to tumor necrosis factor (TNFa).

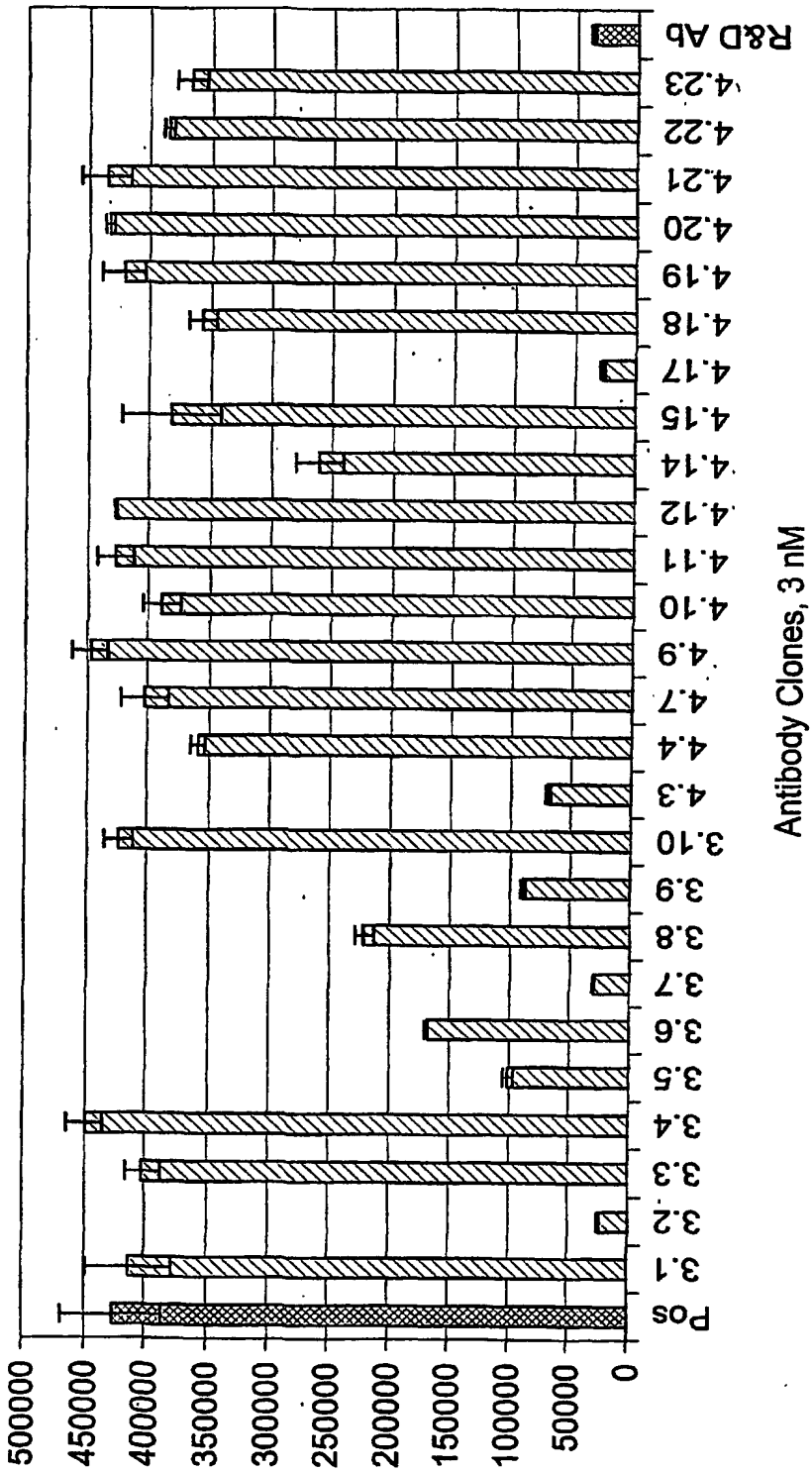


FIG. 1

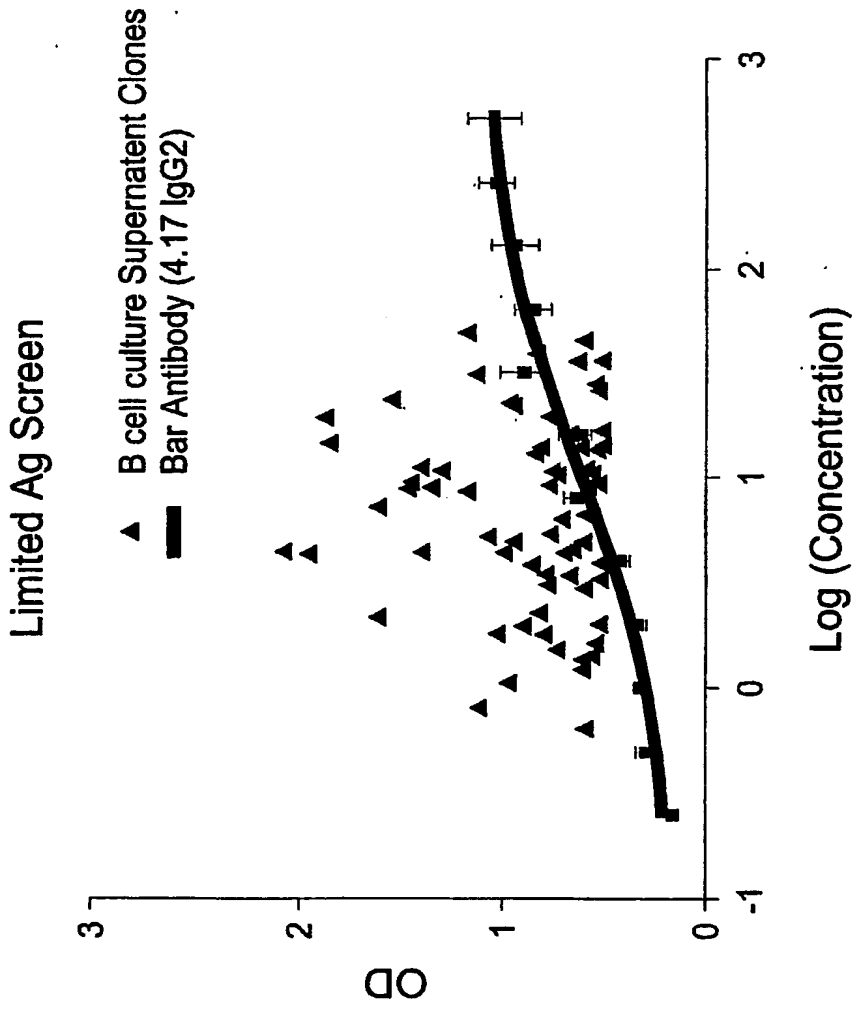


FIG. 2

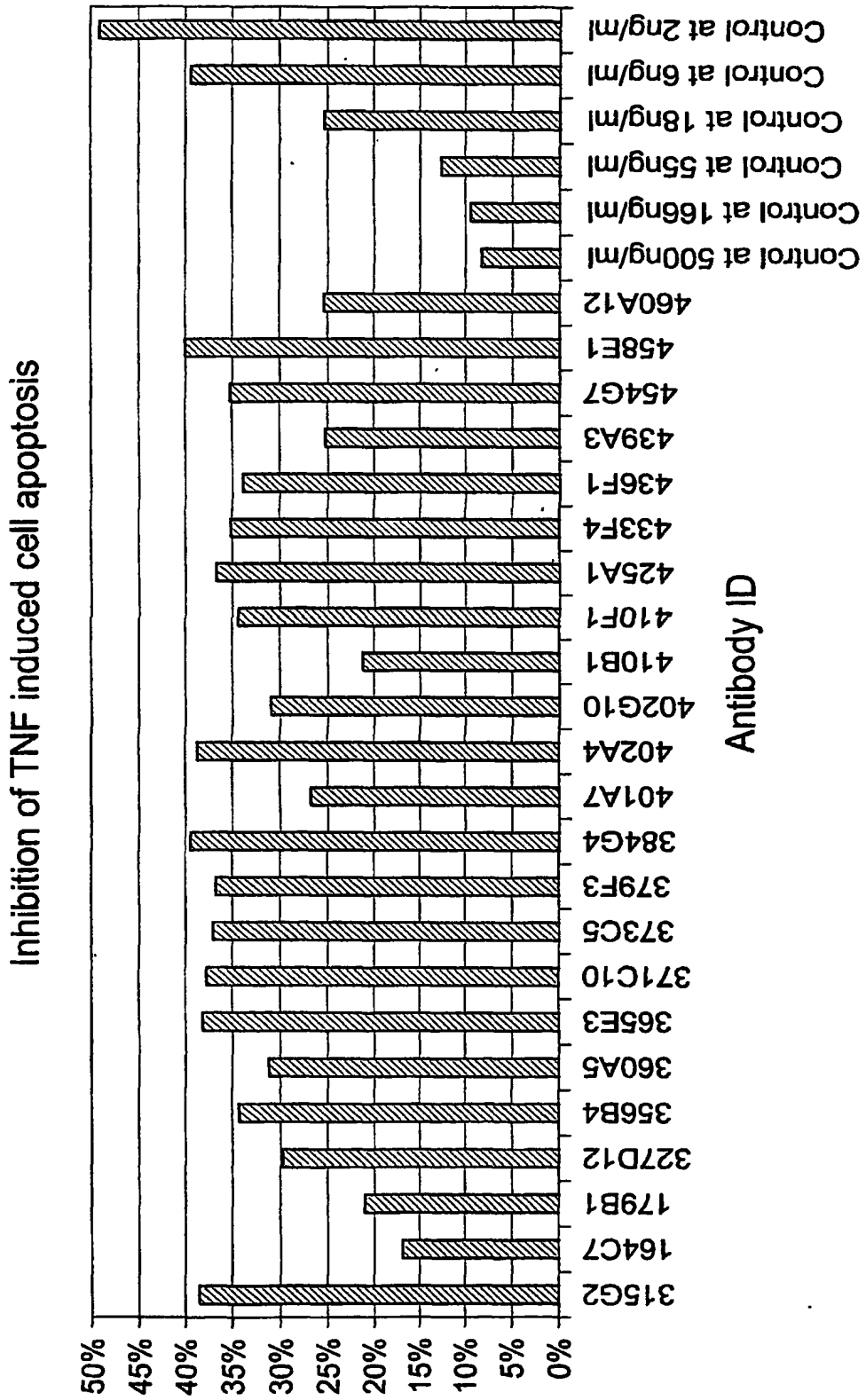


FIG. 3

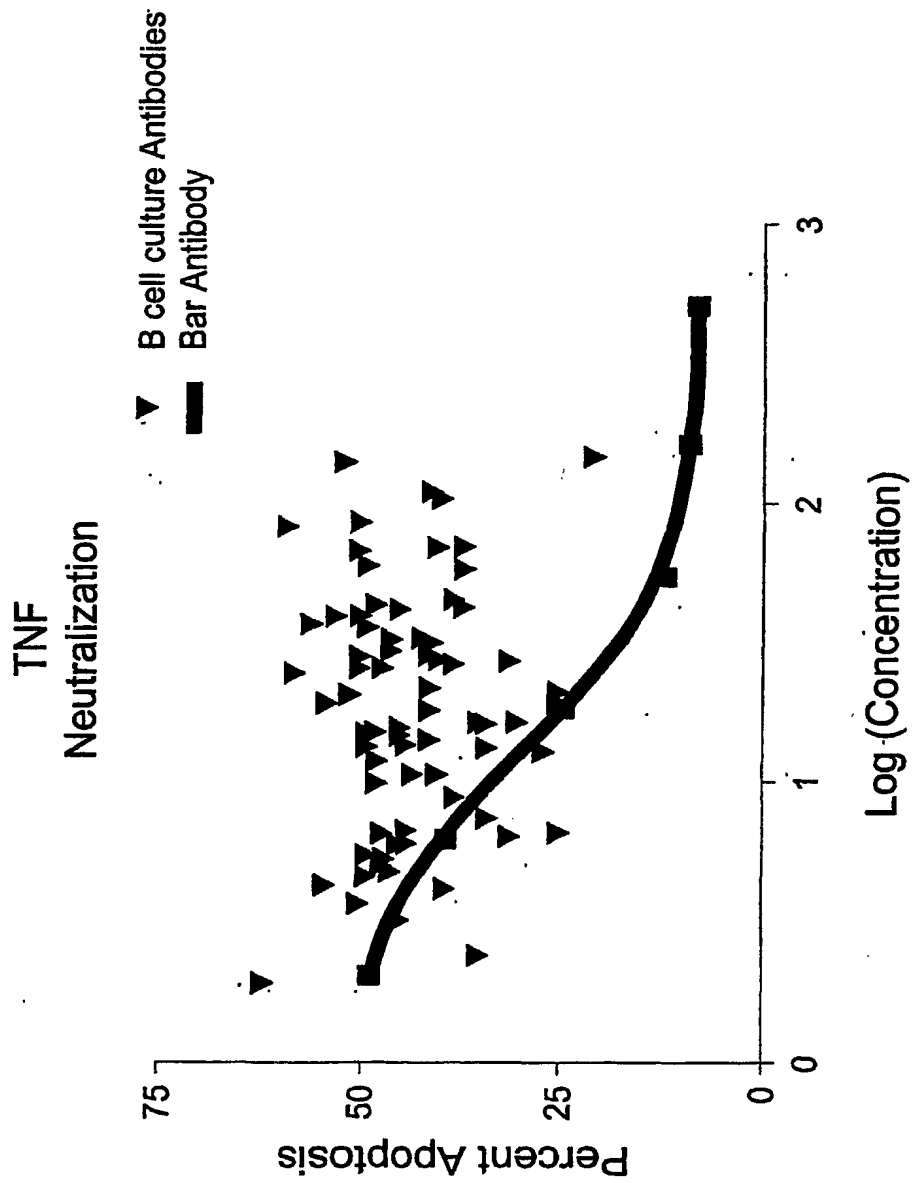


FIG. 4

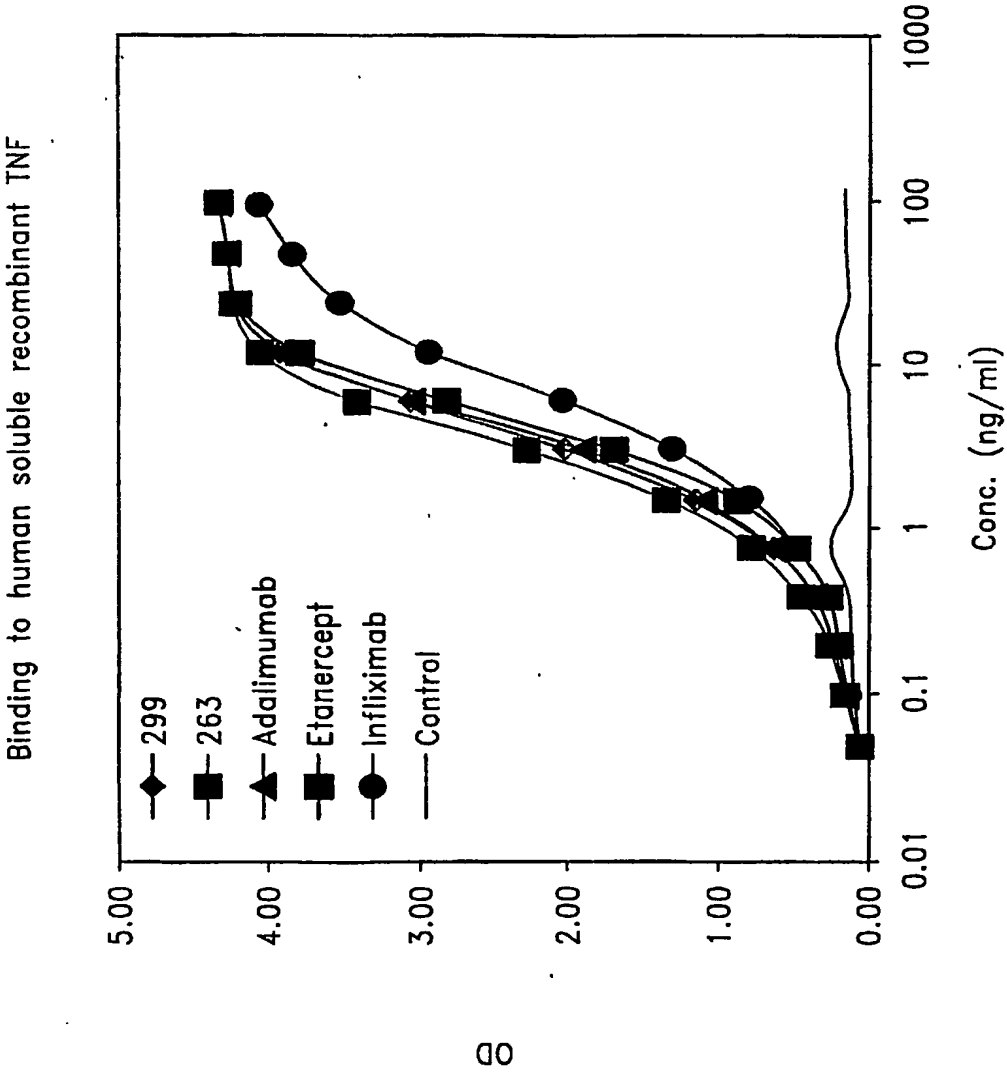


FIG. 5

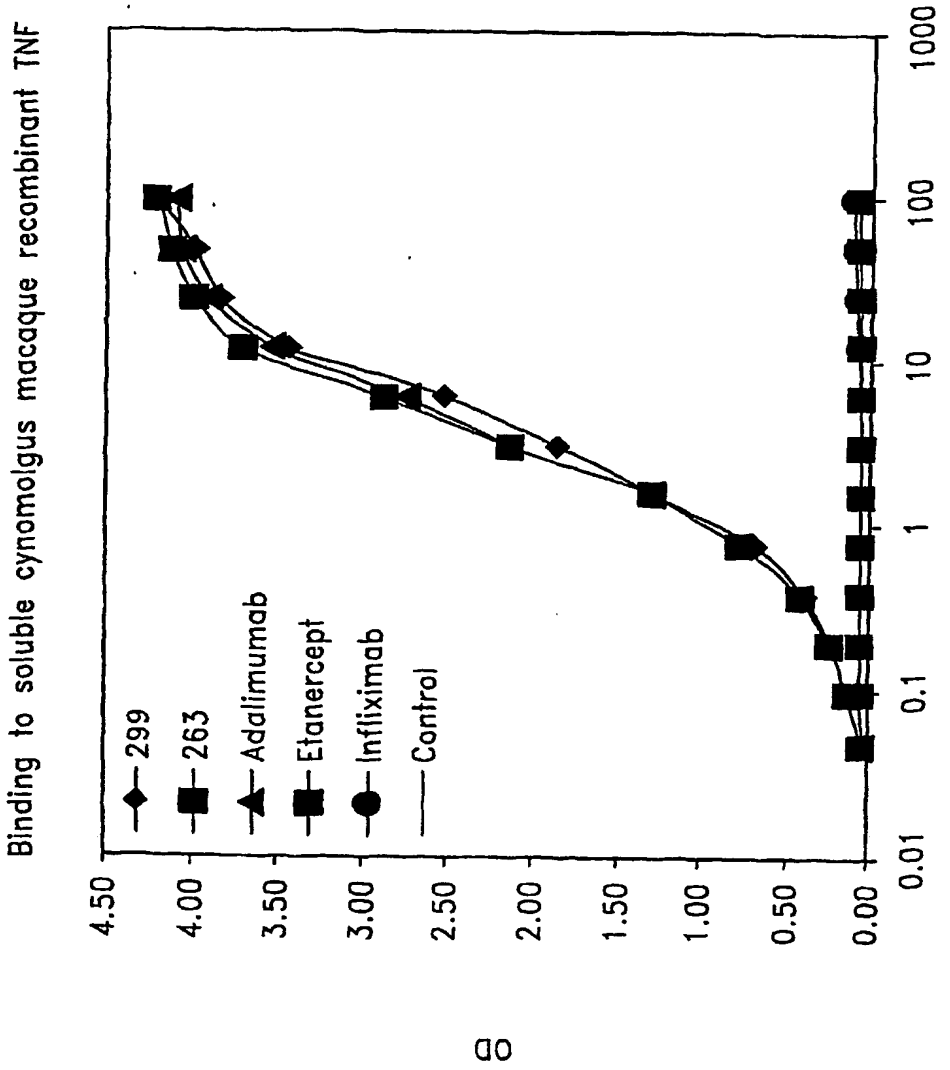


FIG. 6

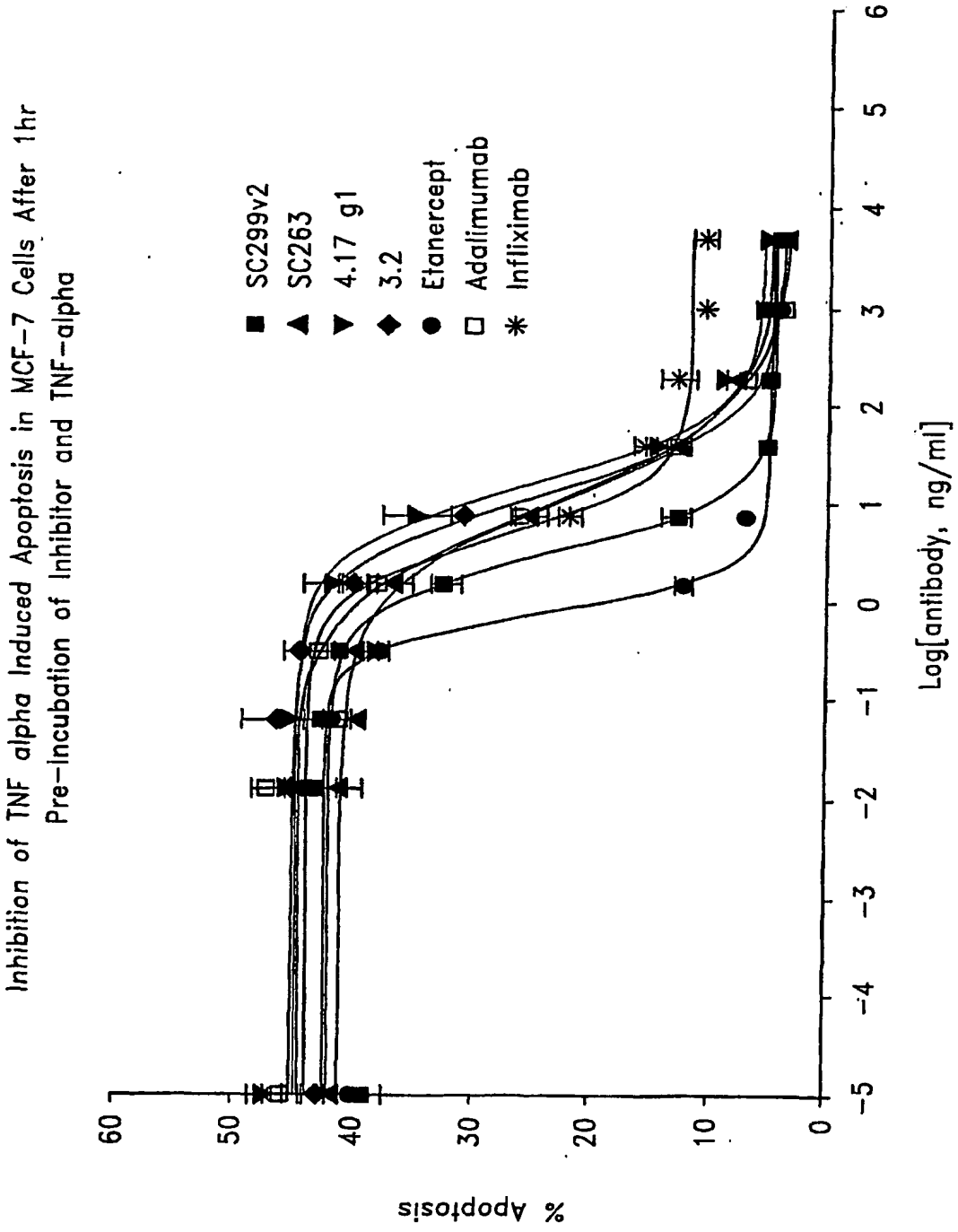


FIG. 7

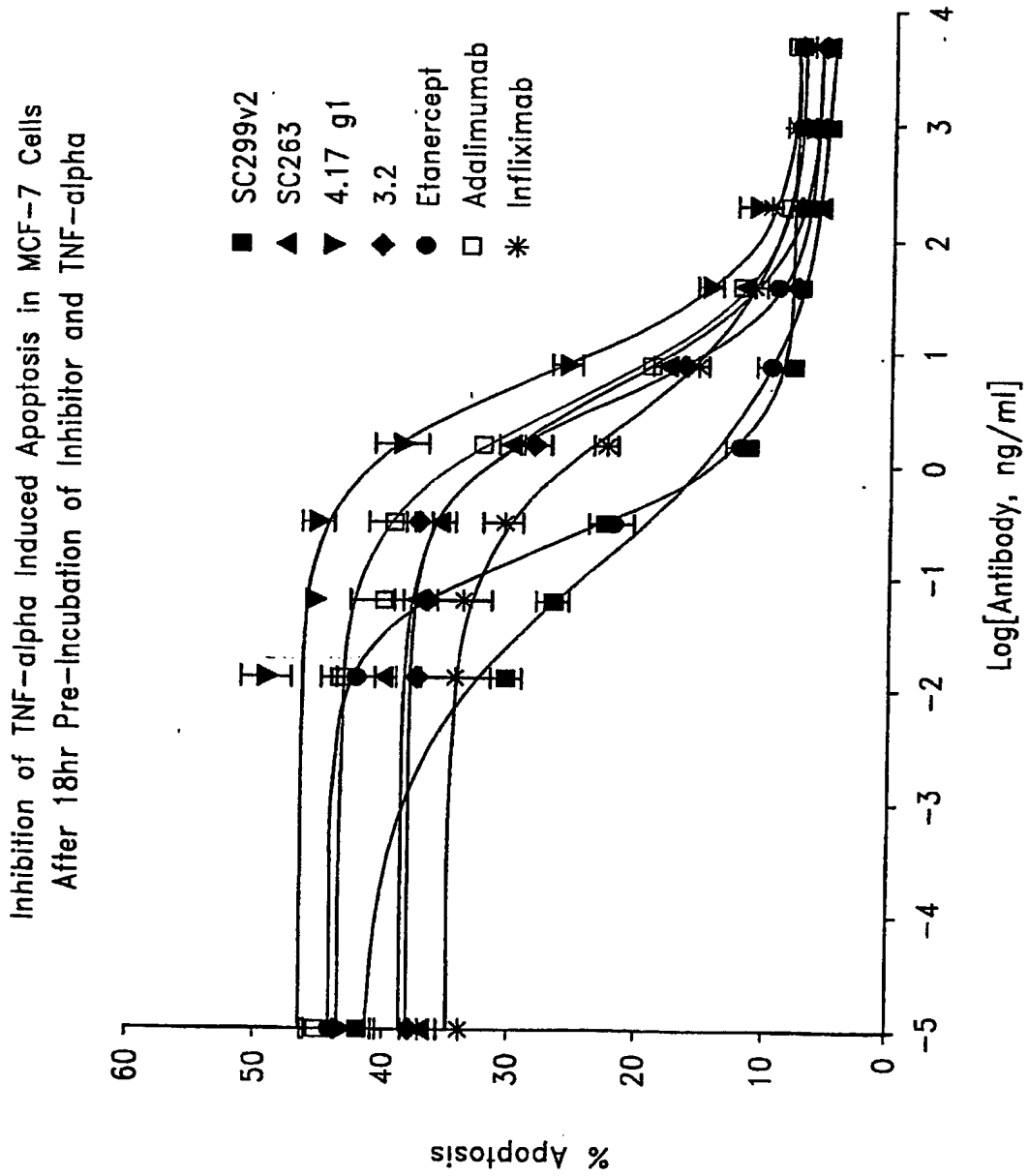


FIG. 8

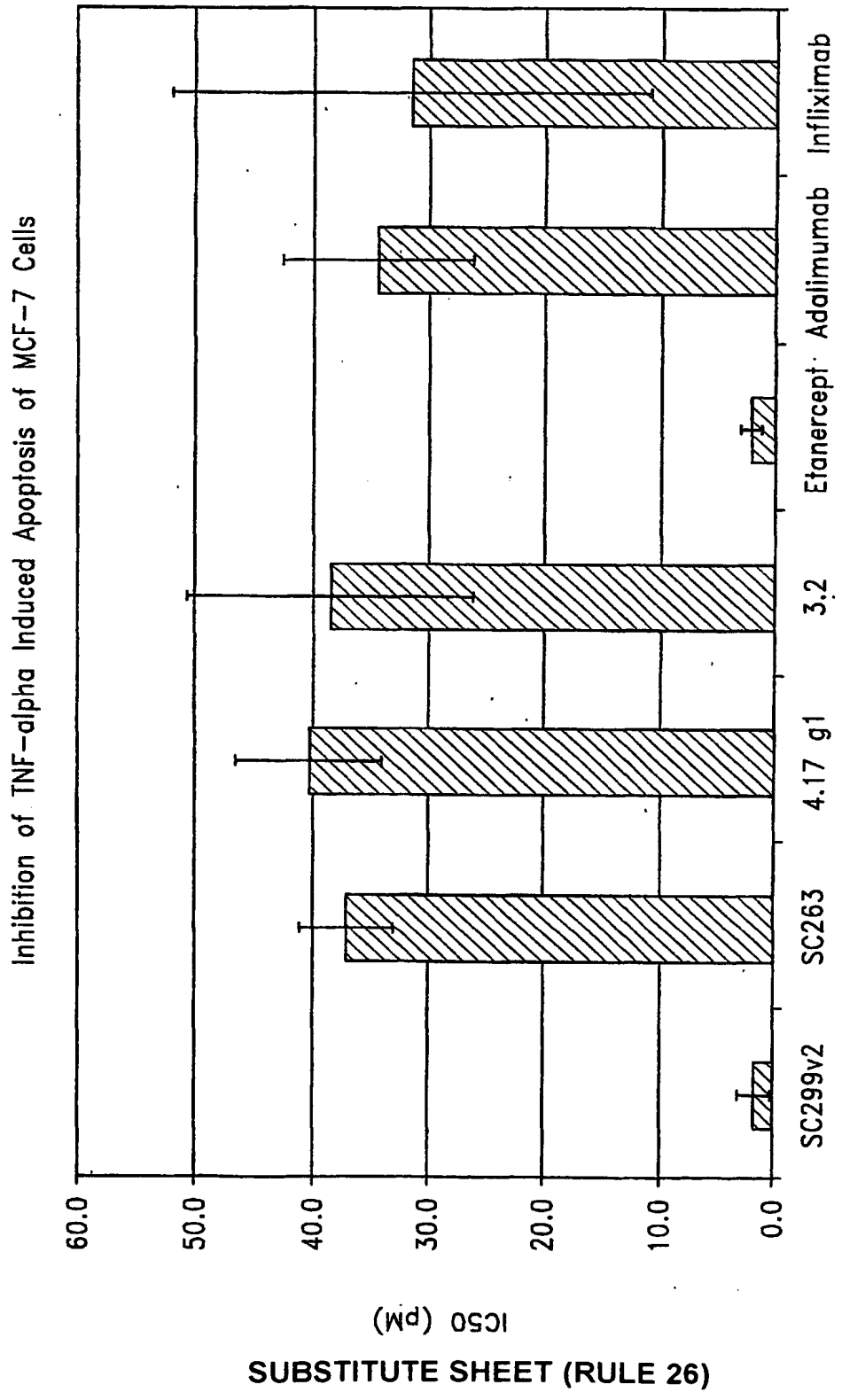


FIG. 9

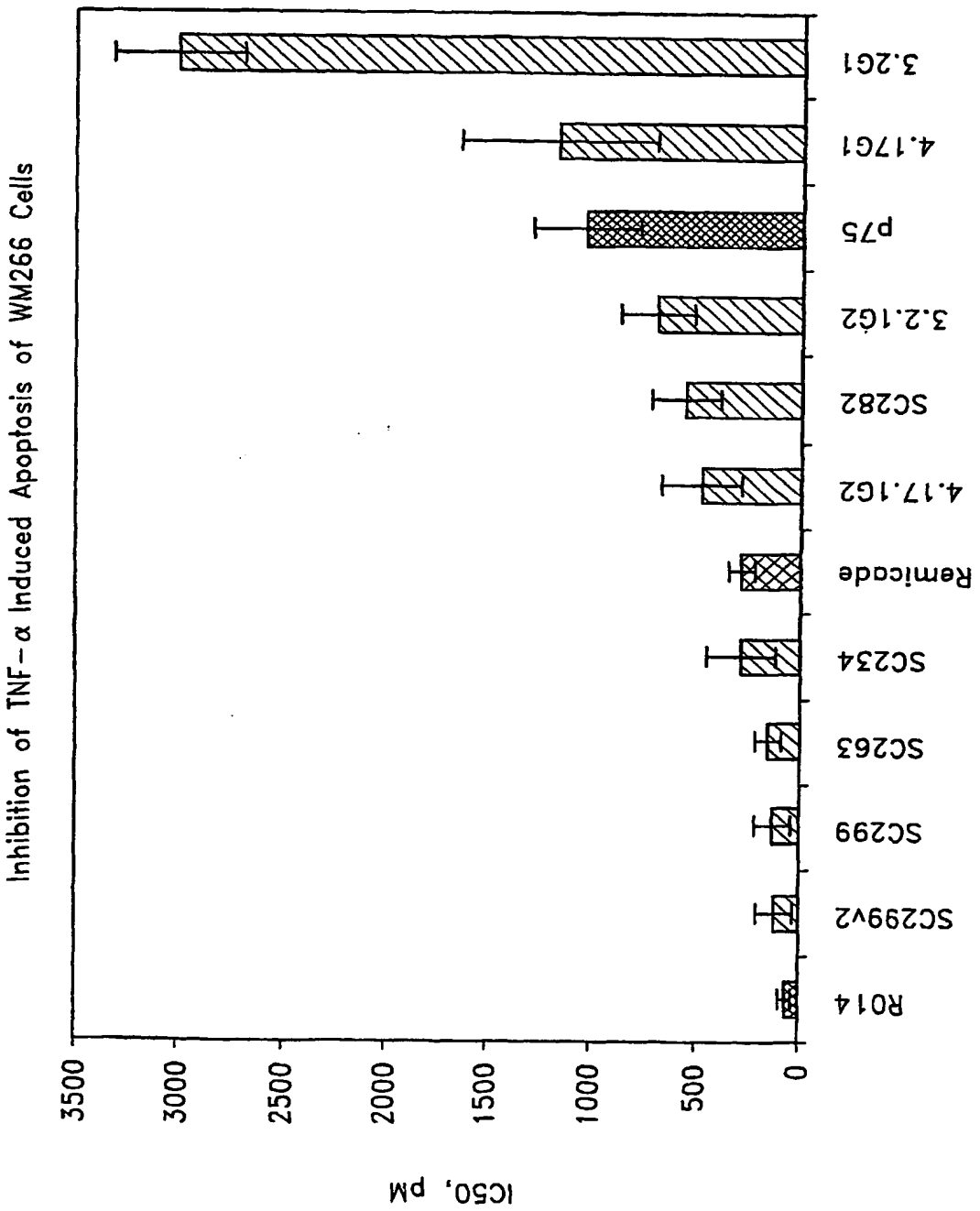


FIG. 10

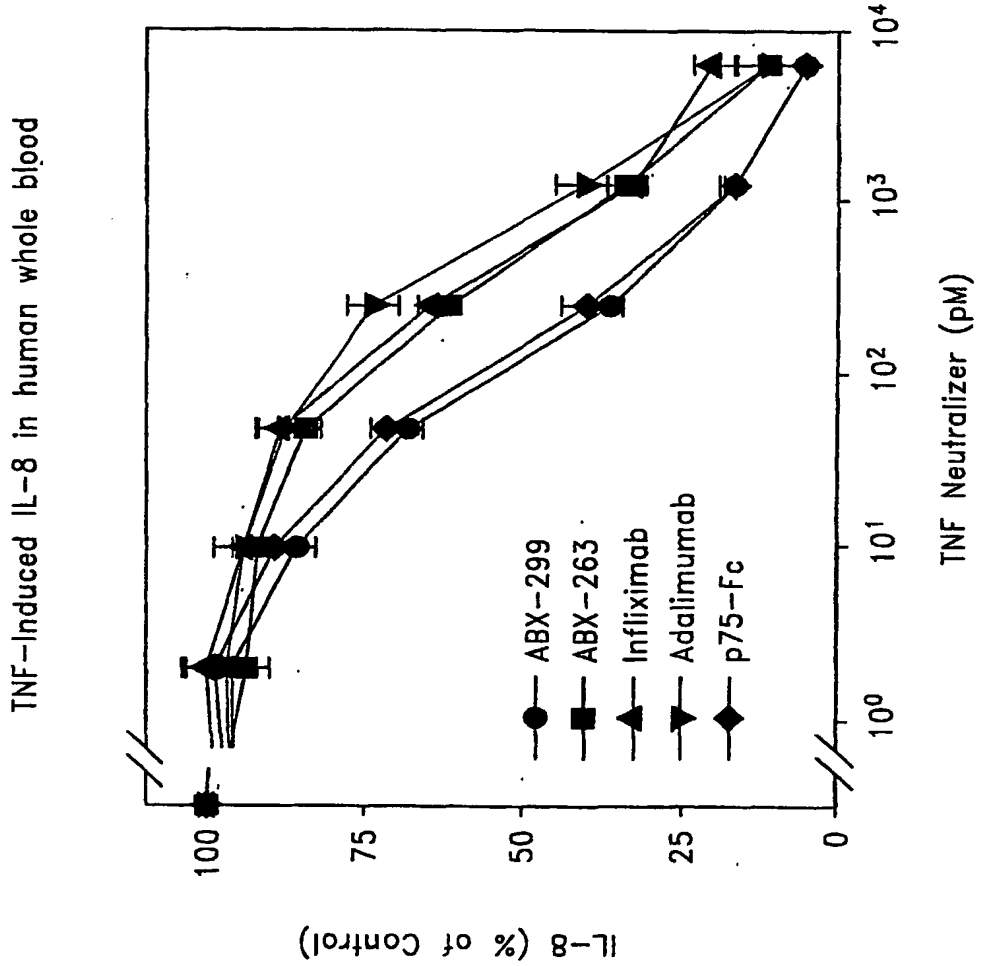


FIG. 11

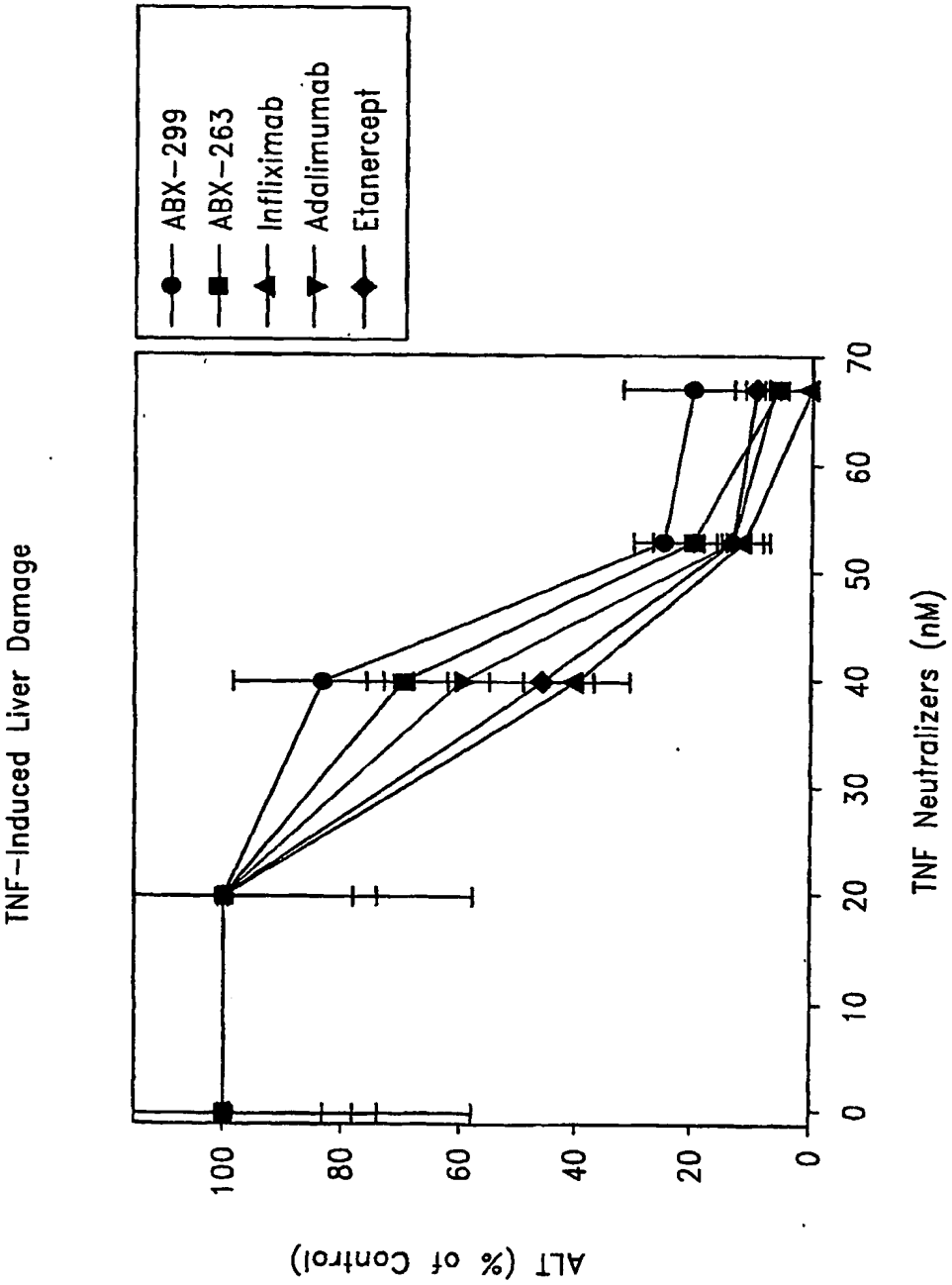


FIG. 12

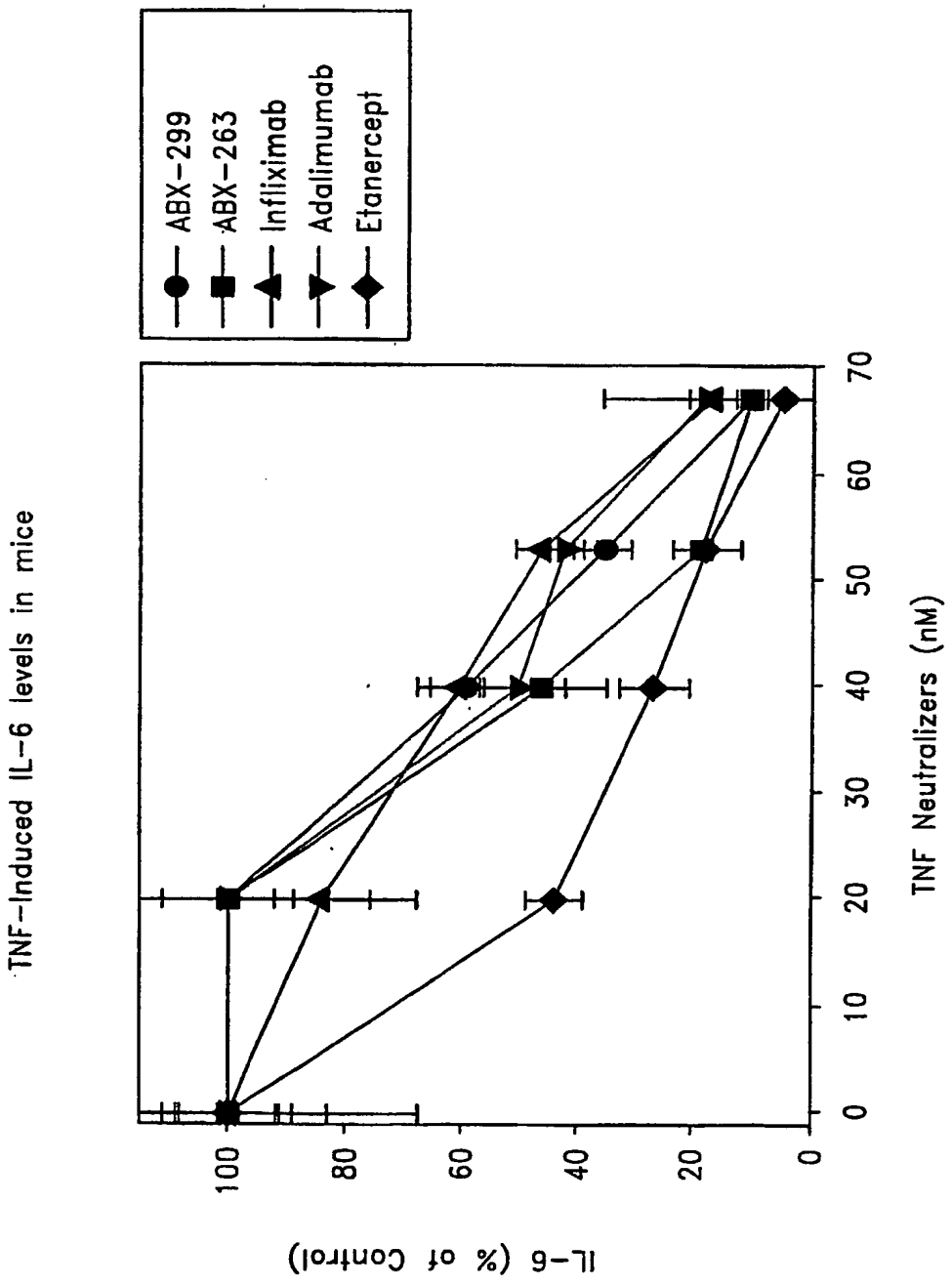


FIG. 13

SEQUENCE LISTING

<110> Abgenix, Inc.
John S. Babcook
Jaspal S. Kang
Orit Foord
Larry Green
Xiao Feng
Scott Klakamp
Mary Haak-Frendscho
Palaniswami Rathanaswami
Craig Pigott
Meina Liang
Rozanne Lee
Kathy Manchulencho
Raffaella Faggioni
Giorgio Senaldi
Qiaojuan Jane Su

<120> ANTIBODIES DIRECTED TO TUMOR NECROSIS FACTOR AND USES THEREOF

<130> ABGENIX.073VPC

<140> Unknown
<141> 2003-12-02

<150> 60/430729
<151> 2002-12-02

<160> 320

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 384
<212> DNA
<213> Homo sapiens

<400> 1
caggtgcagt tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggaacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agtaaccaat ataactggaa cgacgaggtc tacgactacg gtttggacgt ctggggccaa 360
gggaccacgg tcaccgtgtc ctca 384

<210> 2
<211> 128
<212> PRT
<213> Homo sapiens

<400> 2
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

```
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45
Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50                  55                  60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95
Cys Ala Arg Asp Ser Asn Gln Tyr Asn Trp Asn Asp Glu Val Tyr Asp
            100                 105                 110
Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 3
<211> 321
<212> DNA
<213> Homo sapiens

<400> 3
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa cataataatt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 4
<211> 107
<212> PRT
<213> Homo sapiens

<400> 4
```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 5
<211> 375
<212> DNA
<213> Homo sapiens

<400> 5
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgaca ttcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaggag 300
cagctcgtcc ggggagggta ctactactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 6
<211> 125
<212> PRT
<213> Homo sapiens

<400> 6

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Asp	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Ser	Ile	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Glu	Gln	Leu	Val	Arg	Gly	Gly	Tyr	Tyr	Tyr	Tyr	Gly	Met
			100					105					110		
Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
		115					120					125			

<210> 7
<211> 321
<212> DNA
<213> Homo sapiens

<400> 7
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctataggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgtca 180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 8
<211> 107
<212> PRT
<213> Homo sapiens

<400> 8

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Ile	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp
			20					25					30		
Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
		35					40					45			
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Pro	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	His	Asn	Ser	Tyr	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 9
<211> 384
<212> DNA
<213> Homo sapiens

<400> 9
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggaacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agtaaccaat ataactggaa cgacgaggtc tacgactacg gtttggacgt ctggggccaa 360
gggaccacgg tcaccgtgtc ctca 384

<210> 10
<211> 128
<212> PRT
<213> Homo sapiens

<400> 10
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Asp Ser Asn Gln Tyr Asn Trp Asn Asp Glu Val Tyr Asp
100 105 110
Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 11
<211> 321
<212> DNA
<213> Homo sapiens

<400> 11
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaagaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 12
<211> 107
<212> PRT
<213> Homo sapiens

<400> 12
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Arg
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

```
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 13
<211> 369
<212> DNA
<213> Homo sapiens

<400> 13
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgacaatt atatcatatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgt gacgtattac 300
gatttttgga gtggttatct cccaggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 14
<211> 123
<212> PRT
<213> Homo sapiens

<400> 14

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Thr Ile Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Val Thr Tyr Tyr Asp Phe Trp Ser Gly Tyr Leu Pro Gly Met Asp Val
            100                 105                 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 15
<211> 321
<212> DNA
<213> Homo sapiens

<400> 15
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttaa cctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt tcccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 16
<211> 107
<212> PRT
<213> Homo sapiens

<400> 16
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Phe Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 17
<211> 351
<212> DNA
<213> Homo sapiens

<400> 17
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcaat cattactact ggagctggat ccggcagccc 120
gccgggaagg gcctggaatg gattgggcgt atctatccca ctgggagcac caactacaac 180
ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gccgtatatt actgtgcggg cggctggtcg 300
tactggtact tcgatctctg gggccgtggc accctggtca ctgtctcctc a 351

<210> 18
<211> 117
<212> PRT
<213> Homo sapiens

<400> 18
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn His Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Tyr Pro Thr Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Gly Gly Trp Ser Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 19
<211> 342
<212> DNA
<213> Homo sapiens

<400> 19
gatgttgtga tgactcagtc tcctctctcc ctgcccgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaagcaccta cttgaattgg 120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taactgggac 180
tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggctgaaga tgttggggtt tattactgca tgcaaggttc acactggcct 300
cgggagttca ctttcggcgg agggaccaag gtggagatca aa 342

<210> 20
<211> 114
<212> PRT
<213> Homo sapiens

<400> 20
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30
Asp Gly Ser Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Trp Asp Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95
Ser His Trp Pro Arg Glu Phe Thr Phe Gly Gly Gly Thr Lys Val Glu
100 105 110
Ile Lys

<210> 21
<211> 369
<212> DNA
<213> Homo sapiens

<400> 21
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aactatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgcat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagata 300
gcagtggctg gaggttacta ctacggtttg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 22
<211> 123
<212> PRT
<213> Homo sapiens

<400> 22
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

```
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu His
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Ile Ala Val Ala Gly Gly Tyr Tyr Tyr Gly Leu Asp Val
            100                 105                 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 23
<211> 321
<212> DNA
<213> Homo sapiens

<400> 23
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca cagtcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag catcatagtt acccgctcac tttcggcgga 300
gggaccaagg tacagatcaa t 321

<210> 24
<211> 107
<212> PRT
<213> Homo sapiens

<400> 24
```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His His Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Gln Ile Asn
            100                 105
```

<210> 25
<211> 384
<212> DNA
<213> Homo sapiens

<400> 25
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggaacatct attacagtgg gagcacctac 180
tacaccccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agtaaccaat ataactggaa cgacgaggtc tacgactacg gtttggacgt ctggggccaa 360

gggaccacgg tcaccgtgtc ctca 384

<210> 26
<211> 128
<212> PRT
<213> Homo sapiens

<400> 26
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Thr Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Asp Ser Asn Gln Tyr Asn Trp Asn Asp Glu Val Tyr Asp
100 105 110
Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 27
<211> 321
<212> DNA
<213> Homo sapiens

<400> 27
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataataatt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 28
<211> 107
<212> PRT
<213> Homo sapiens

<400> 28
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 29
<211> 384
<212> DNA
<213> Homo sapiens

<400> 29
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggaacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agtaaccagt ataactggaa cgacgaggtc tacgactacg gtttggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 30
<211> 128
<212> PRT
<213> Homo sapiens

<400> 30
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Asp Ser Asn Gln Tyr Asn Trp Asn Asp Glu Val Tyr Asp
100 105 110
Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 31
<211> 321
<212> DNA
<213> Homo sapiens

<400> 31
gacatccaaa tgacccagtc tccatccgcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcttcag cataaaagtt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 32
<211> 107
<212> PRT
<213> Homo sapiens

<400> 32
Asp Ile Gln Met Thr Gln Ser Pro Ser Ala Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

```
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 33
<211> 366
<212> DNA
<213> Homo sapiens

<400> 33
caggtgcagc tggtggagtc tgggggaggt gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagatcag 300
gataactgga actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 34
<211> 122
<212> PRT
<213> Homo sapiens

<400> 34
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Asp Asn Trp Asn Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 35
<211> 333
<212> DNA
<213> Homo sapiens

<400> 35
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctt catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctcctgatct ttttgggttc ttatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaacttgg 300

acgttcggcc aagggaccaa ggtggaaatc aaa 333

<210> 36
<211> 111
<212> PRT
<213> Homo sapiens

<400> 36

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5					10					15	
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
			20					25					30		
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35					40					45			
Pro	Gln	Leu	Leu	Ile	Phe	Leu	Gly	Ser	Tyr	Arg	Ala	Ser	Gly	Val	Pro
	50					55					60				
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70					75					80
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
				85					90					95	
Leu	Gln	Thr	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	
			100					105					110		

<210> 37
<211> 372
<212> DNA
<213> Homo sapiens

<400> 37
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aactatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt atttctgtgc gagagagaca 300
gctatcctta ggggctacta ctactacgat atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 38
<211> 124
<212> PRT
<213> Homo sapiens

<400> 38

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Tyr
			20					25					30		
Asp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Ser	Ile	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys
				85					90					95	
Ala	Arg	Glu	Thr	Ala	Ile	Leu	Arg	Gly	Tyr	Tyr	Tyr	Tyr	Asp	Met	Asp
			100					105					110		
Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				
		115					120								

<210> 39
<211> 321
<212> DNA
<213> Homo sapiens

<400> 39
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctctgct gcatccagtt tgcaaggtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 40
<211> 107
<212> PRT
<213> Homo sapiens

<400> 40
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Ser Ala Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 41
<211> 372
<212> DNA
<213> Homo sapiens

<400> 41
caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaagtga acagcctgag agctgaggac acggctgtgt attactgtgc gagagaggtc 300
cgtagtggga gctactacta ttactacagt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 42
<211> 124
<212> PRT
<213> Homo sapiens

<400> 42
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45
Ala Val Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Val Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Val Arg Ser Gly Ser Tyr Tyr Tyr Tyr Tyr Ser Met Asp
            100                 105                 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 43
<211> 321
<212> DNA
<213> Homo sapiens

<400> 43
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacatcaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcgtccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa cataatagtt atccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 44
<211> 107
<212> PRT
<213> Homo sapiens

<400> 44

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 45
<211> 345
<212> DNA
<213> Homo sapiens

<400> 45
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggaatg ggtctcagtt atttatagcg gtgataggac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgcg aggggagggg 300
ggatttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 46
<211> 115
<212> PRT
<213> Homo sapiens

<400> 46
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Glu Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ser
115

<210> 47
<211> 318
<212> DNA
<213> Homo sapiens

<400> 47
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttacc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccagactcct catccatggt gcatccatta gggccactgg tctcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagtag cctgcagtct 240
gaagattttg cagtctatta ctgtcagcag tataattatt ggtggacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 48
<211> 106
<212> PRT
<213> Homo sapiens

<400> 48
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
His Gly Ala Ser Ile Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Tyr Trp Trp Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 49
<211> 345

<212> DNA
<213> Homo sapiens

<400> 49
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt aggaactaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggaatg ggtctcagtt atttatagcg gtgataggac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgcg aggggagggg 300
ggatttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 50
<211> 115
<212> PRT
<213> Homo sapiens

<400> 50
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Arg Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Glu Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ser
115

<210> 51
<211> 318
<212> DNA
<213> Homo sapiens

<400> 51
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccagactcct catccatggt gcatccatta gggccactgg tctcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagtag cctccagtct 240
gaagattttg cagtctatta ctgtcagcag tataattatt ggtggacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 52
<211> 106
<212> PRT
<213> Homo sapiens

<400> 52
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
His Gly Ala Ser Ile Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly

```
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Tyr Trp Trp Thr
                85                  90                  95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 53
<211> 345
<212> DNA
<213> Homo sapiens

<400> 53
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgagtt caccgtcagt aggaactaca tgagctgggt ccgccaggct 120
ccagggaagg gactggaatg ggtctcagtt atttatagcg gtgataggac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgcg aggggagggg 300
ggatttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 54
<211> 115
<212> PRT
<213> Homo sapiens

<400> 54

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Phe Thr Val Ser Arg Asn
            20                  25                  30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Gly Glu Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110
Val Ser Ser
        115
```

<210> 55
<211> 318
<212> DNA
<213> Homo sapiens

<400> 55
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccagactcct catccatggt gcatccatta gggccactgg tctcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagtag cctgcagtct 240
gaagattttg cagtctatta ctgtcagcag tataattatt ggtggacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 56
<211> 106

<212> PRT
<213> Homo sapiens

<400> 56
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
His Gly Ala Ser Ile Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Tyr Trp Trp Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 57
<211> 375
<212> DNA
<213> Homo sapiens

<400> 57
caggtgcaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccgtcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtcta atggaagtaa taagtactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagataac 300
ggtgtctacg tgggatacgc ctactattac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 58
<211> 125
<212> PRT
<213> Homo sapiens

<400> 58
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Ser Asn Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Asn Gly Val Tyr Val Gly Tyr Ala Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 59
<211> 321
<212> DNA

<213> Homo sapiens

<400> 59
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 60
<211> 107
<212> PRT
<213> Homo sapiens

<400> 60
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Arg
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 61
<211> 375
<212> DNA
<213> Homo sapiens

<400> 61
caggtgcaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccgtcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtcta atggaagtaa taagtactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagataac 300
ggtgtctacg tgggatacgc ctactattac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 62
<211> 125
<212> PRT
<213> Homo sapiens

<400> 62
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Ser Asn Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Asn Gly Val Tyr Val Gly Tyr Ala Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 63
<211> 321
<212> DNA
<213> Homo sapiens

<400> 63
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcaaaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcacagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa cataatagtt acccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 64
<211> 107
<212> PRT
<213> Homo sapiens

<400> 64
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 65
<211> 384
<212> DNA
<213> Homo sapiens

<400> 65
caggtgcagc tggtggagtc tgggggaagc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aactatggca tacactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtctg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagctc 300
ccgaatagtg ggagctactc cggttactac tactactacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 66
<211> 128
<212> PRT

<213> Homo sapiens

<400> 66

```
Gln Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30
Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Ser Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Leu Pro Asn Ser Gly Ser Tyr Ser Gly Tyr Tyr Tyr Tyr
            100                 105                 110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 67
<211> 321
<212> DNA
<213> Homo sapiens

<400> 67

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cattgttgtt accctctcac tttcggcgga 300
gggaccaagg tggaaatcaa a                                          321
```

<210> 68
<211> 107
<212> PRT
<213> Homo sapiens

<400> 68

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Cys Cys Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 69
<211> 375
<212> DNA
<213> Homo sapiens

<400> 69
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtctg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaagtg 300
gaatcagcta tgggagggtt ctactacaac ggtatggacg tctggggcca aggggccacg 360
gtcaccgtct cctca 375

<210> 70
<211> 125
<212> PRT
<213> Homo sapiens

<400> 70
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Ala Thr Val Thr Val Ser Ser
115 120 125

<210> 71
<211> 321
<212> DNA
<213> Homo sapiens

<400> 71
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtagggga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga attgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc ggggacagaa ttcattttca caatcagcag cctgcagcct 240
gaagattttg caagttatta ctgtctacag cataaaagtt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 72
<211> 107
<212> PRT
<213> Homo sapiens

<400> 72
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ile Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Ile Phe Thr Ile Ser Ser Leu Gln Pro

65 70 75 80
Glu Asp Phe Ala Ser Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 73
<211> 375
<212> DNA
<213> Homo sapiens

<400> 73
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtctg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaagtg 300
gaatcagcta tgggagggtt ctactacaac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 74
<211> 125
<212> PRT
<213> Homo sapiens

<400> 74
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 75
<211> 375
<212> DNA
<213> Homo sapiens

<400> 75
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aaccatgaca tacactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtctg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaag 300
atggctacaa ttaaggggta ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 76
<211> 125

<212> PRT
<213> Homo sapiens

<400> 76
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
20 25 30
Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Ser Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Lys Met Ala Thr Ile Lys Gly Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 77
<211> 321
<212> DNA
<213> Homo sapiens

<400> 77
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tggaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcca a 321

<210> 78
<211> 107
<212> PRT
<213> Homo sapiens

<400> 78
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Gln
100 105

<210> 79
<211> 336
<212> DNA
<213> Oryctolagus cuniculus

<400> 79
cagtcactgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgcacagtct ctggaatcga cctcagtagc aatacaatgg gctggttccg ccgggctcca 120
gggaaggggc tggagtggat cggaatcatt attagtagtg gtaccacata ctacgcgagc 180
tgggtaaaag gccgattcac catctccaaa acctcgacca cggtggatct gaaaatcacc 240
cgtccgacaa ccgaggacac ggccacatat ttctgtgcca gaggctggta cgagtttaac 300
ttgtggggcc caggcaccct ggtcaccgtc tcctca 336

<210> 80
<211> 112
<212> PRT
<213> Oryctolagus cuniculus

<400> 80
Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15
Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Asn Thr
20 25 30
Met Gly Trp Phe Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45
Ile Ile Ile Ser Ser Gly Thr Thr Tyr Tyr Ala Ser Trp Val Lys Gly
50 55 60
Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu Lys Ile Thr
65 70 75 80
Arg Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly Trp
85 90 95
Tyr Glu Phe Asn Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 81
<211> 339
<212> DNA
<213> Oryctolagus cuniculus

<400> 81
gatgttgtga tgacccagac tccagcctcc gtggaggcag ctgtgggagg cacagtcacc 60
atcaagtgcc aggccagtga gaacattgat atcttattgg cctggtatca gcagaaagta 120
gggcagcctc ccaagctcct gatctatagg gcatccaaac tggcctctgg ggccccatcg 180
cggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcga cctggagtgt 240
ggcgatgctg ccacttacta ctgtcaaagc aatgttggta gtactgctag aagtagttat 300
ggtaatgctt tcggcggagg gaccgaggtg gtggtcaaa 339

<210> 82
<211> 113
<212> PRT
<213> Oryctolagus cuniculus

<400> 82
Asp Val Val Met Thr Gln Thr Pro Ala Ser Val Glu Ala Ala Val Gly
1 5 10 15
Gly Thr Val Thr Ile Lys Cys Gln Ala Ser Glu Asn Ile Asp Ile Leu
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Val Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Arg Ala Ser Lys Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Asp Leu Glu Cys
65 70 75 80
Gly Asp Ala Ala Thr Tyr Tyr Cys Gln Ser Asn Val Gly Ser Thr Ala

```
                85                  90                  95
Arg Ser Ser Tyr Gly Asn Ala Phe Gly Gly Gly Thr Glu Val Val Val
            100                 105                 110
Lys
```

<210> 83
<211> 348
<212> DNA
<213> Homo sapiens

<400> 83
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagaa gtggtagtac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatcttta 300
ggcggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctca 348

<210> 84
<211> 116
<212> PRT
<213> Homo sapiens

<400> 84
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110
Thr Val Ser Ser
        115
```

<210> 85
<211> 330
<212> DNA
<213> Homo sapiens

<400> 85
cagtctgtgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc 60
tcctgctctg gaagcagctc caacattggg aataattatg tatcctggta ccagcagttc 120
ccaggaacag cccccaaact cctcatttat gacaataata gccgaccctc agggattcct 180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag 240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgctggggtg 300
ttcggcggag ggaccaagct gaccgtccta 330

<210> 86
<211> 110
<212> PRT
<213> Homo sapiens

<400> 86
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30
Tyr Val Ser Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Asp Asn Asn Ser Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65 70 75 80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
85 90 95
Ser Ala Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 87
<211> 354
<212> DNA
<213> Homo sapiens

<400> 87
caggtgcagc tggtggagtc tgggggagac gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctctggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcaatt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatgac 300
tactactacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> 88
<211> 118
<212> PRT
<213> Homo sapiens

<400> 88
Gln Val Gln Leu Val Glu Ser Gly Gly Asp Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ser
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Asp Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 89
<211> 330
<212> DNA
<213> Homo sapiens

<400> 89

cagtctgcgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc 60
tcctgctctg gaagcagctc caacattggg agtaattatg tatcctggtg ccagcagctc 120
ccaagaacag cccccaaact cctcatttat gacaataata agcgaccctc agggattcct 180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tggtcatcac cggactccag 240
actggggacg aggccgatta ttactgcgga gcatgggata gcagcctgag tgctggggta 300
ttcggcggag ggaccaagct gaccgtccta 330

<210> 90
<211> 110
<212> PRT
<213> Homo sapiens

<400> 90
Gln Ser Ala Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30
Tyr Val Ser Trp Cys Gln Gln Leu Pro Arg Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Val Ile Thr Gly Leu Gln
65 70 75 80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Trp Asp Ser Ser Leu
85 90 95
Ser Ala Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 91
<211> 363
<212> DNA
<213> Homo sapiens

<400> 91
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaaataa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctatat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagagc 300
gactacggtg gtaaccctta ctttgactac tggggccaag ggaccctggt caccgtctcc 360
tca 363

<210> 92
<211> 121
<212> PRT
<213> Homo sapiens

<400> 92
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Asp Tyr Gly Gly Asn Pro Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 93
<211> 324
<212> DNA
<213> Homo sapiens

<400> 93
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaagctat tatgcaagct ggtaccagca gaggccagga 120
caggcccctg tacttgtcat ctatggtaga aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg actcacagct tccttgaccg tcactggggc tcaggcggaa 240
gatgaggctg actattactg taactcccgg gacagcagtt ataaccatgt ggcattcggc 300
ggagggacca agctgaccgt ccta 324

<210> 94
<211> 108
<212> PRT
<213> Homo sapiens

<400> 94
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Arg Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Leu Thr Ala Ser Leu Thr Val Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Tyr Asn His
85 90 95
Val Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 95
<211> 363
<212> DNA
<213> Homo sapiens

<400> 95
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgaactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
ggagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
gtgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagagc 300
gactacggtg gtaaccctta ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 96
<211> 121
<212> PRT
<213> Homo sapiens

<400> 96

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Ser Asp Tyr Gly Gly Asn Pro Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 97
<211> 324
<212> DNA
<213> Homo sapiens

<400> 97
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaatctat tatgcaagct ggtaccagca gaagccagga 120
caggcccctg tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgaccg tcactggggc tcaggcggaa 240
gatgaggctg actattactg taagtcccgg gacagcagtt ttaaccatgt gacattcggc 300
ggagggacca agctgaccgt ccta 324

<210> 98
<211> 108
<212> PRT
<213> Homo sapiens

<400> 98

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ile Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Val Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ser Ser Phe Asn His
                85                  90                  95
Val Thr Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 99
<211> 348
<212> DNA
<213> Homo sapiens

<400> 99
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agtgactgga tcggctgggt gcgccagatg 120

cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gaggagtggt 300
tacggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctca 348

<210> 100
<211> 116
<212> PRT
<213> Homo sapiens

<400> 100
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Asp
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Ser Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110
Thr Val Ser Ser
115

<210> 101
<211> 334
<212> DNA
<213> Homo sapiens

<400> 101
cagtctctgc tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60
tcctgcactg ggagcagctc caacatcggg gcaggttatg atgtacactg gtaccagcag 120
tttccaggaa cagcccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240
caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300
gtattcggcg gagggaccaa gctgaccgtc ctag 334

<210> 102
<211> 111
<212> PRT
<213> Homo sapiens

<400> 102
Gln Ser Leu Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

100 105 110

<210> 103
<211> 375
<212> DNA
<213> Homo sapiens

<400> 103
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt taccttcagt agttatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaataccat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaat 300
actatggttc ggggggggga ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 104
<211> 125
<212> PRT
<213> Homo sapiens

<400> 104
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr His Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Asn Thr Met Val Arg Gly Gly Asp Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 105
<211> 324
<212> DNA
<213> Homo sapiens

<400> 105
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaaggtat tatgcaagct ggtaccagca gaagccagga 120
caggccccta tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taactcccgg gacagcagtg gtaaccatct ggtgttcggc 300
ggagggacca agctgaccgt ccta 324

<210> 106
<211> 108
<212> PRT
<213> Homo sapiens

<400> 106
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln

```
 1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Arg Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
                85                  90                  95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 107
<211> 366
<212> DNA
<213> Homo sapiens

<400> 107
caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgttaa cacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgaa cacagcctac 240
atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcct 300
ataactgaaa ctatggagga ctactttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca 366

<210> 108
<211> 122
<212> PRT
<213> Homo sapiens

<400> 108
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Ser Ala Tyr Asn Val Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Pro Ile Thr Glu Thr Met Glu Asp Tyr Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 109
<211> 324
<212> DNA
<213> Homo sapiens

<400> 109
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaaactat tatgcaagtt ggtaccagca gaagccagga 120

caggccccta tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taactcccgg gacagcagtg gtaatcatct ggtattcggc 300
ggagggacca agttgaccgt ccta 324

<210> 110
<211> 107
<212> PRT
<213> Homo sapiens

<400> 110
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Asn Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val
100 105

<210> 111
<211> 366
<212> DNA
<213> Homo sapiens

<400> 111
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagaaa taaatacaat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgaat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattta 300
acgtattacg atattttggg cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 112
<211> 122
<212> PRT
<213> Homo sapiens

<400> 112
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Tyr Asn Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Thr Tyr Tyr Asp Ile Leu Gly Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 113
<211> 333
<212> DNA
<213> Homo sapiens

<400> 113
cagtctgtgc tgacgcagtc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60
tcctgcactg ggagcagctc caacatcggg gcaggttatg atgtacactg gtaccagcag 120
cttccaggaa cagcccccag actcctcatc tatggtaaca acaatcgtcc ctcaggggtc 180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240
caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300
gtgttcggcg gagggaccaa gctgaccgtc cta 333

<210> 114
<211> 111
<212> PRT
<213> Homo sapiens

<400> 114
Gln Ser Val Leu Thr Gln Ser Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Arg Leu
35 40 45
Leu Ile Tyr Gly Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 115
<211> 366
<212> DNA
<213> Homo sapiens

<400> 115
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagaaa taaatacaat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgaat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattta 300
acgtattacg atattttggg cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 116
<211> 122
<212> PRT
<213> Homo sapiens

<400> 116
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Tyr Asn Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Leu Thr Tyr Tyr Asp Ile Leu Gly Gly Met Asp Val Trp
            100                 105                 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 117
<211> 324
<212> DNA
<213> Homo sapiens

<400> 117
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaagatat tatgcaagct ggtaccagca gaagccagga 120
caggccccta tagttgtcat ctatggtaaa aaaaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taagtcccgg gacagcagtg gtaaccatct ggtattcggc 300
ggagggacca agctgaccgt ccta 324

<210> 118
<211> 108
<212> PRT
<213> Homo sapiens

<400> 118

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Arg Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Val Val Ile Tyr
        35                  40                  45
Gly Lys Lys Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ser Ser Gly Asn His
                85                  90                  95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 119
<211> 345
<212> DNA
<213> Homo sapiens

<400> 119
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccgccaggct 120
ccagggaagg gtctggagtg ggtctcagtt atttatagcg gtggtggcac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240

caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aggaccgggg 300
tcctttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 120
<211> 115
<212> PRT
<213> Homo sapiens

<400> 120
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Pro Gly Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ser
115

<210> 121
<211> 321
<212> DNA
<213> Homo sapiens

<400> 121
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat tttactctca ccatcagcag cctgcagcct 240
gaagattttg caagttacta ttgtcaacag gctaacagtt tcccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 122
<211> 107
<212> PRT
<213> Homo sapiens

<400> 122
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 123
<211> 369
<212> DNA
<213> Homo sapiens

<400> 123
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagcgg 300
gatagcagtg gctggtacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 124
<211> 123
<212> PRT
<213> Homo sapiens

<400> 124
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Arg Asp Ser Ser Gly Trp Tyr Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 125
<211> 321
<212> DNA
<213> Homo sapiens

<400> 125
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca cagtcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtc tcccgctcac tttcggcgga 300
gggaccaagg ttgagatcaa a 321

<210> 126
<211> 107
<212> PRT
<213> Homo sapiens

<400> 126
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp

```
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Leu Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 127
<211> 378
<212> DNA
<213> Homo sapiens

<400> 127
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300
atagcagtgg ctggtcctcc ttactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

<210> 128
<211> 126
<212> PRT
<213> Homo sapiens

<400> 128
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Gly Ile Ala Val Ala Gly Pro Pro Tyr Tyr Tyr Tyr Gly
            100                 105                 110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 129
<211> 318
<212> DNA
<213> Homo sapiens

<400> 129
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240

gaagatattg caacatatta ctgtcaccag tgtgataatc tccctcactt cggccaaggg 300
acacgactgg agattaaa 318

<210> 130
<211> 106
<212> PRT
<213> Homo sapiens

<400> 130
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys His Gln Cys Asp Asn Leu Pro His
85 90 95
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 131
<211> 369
<212> DNA
<213> Homo sapiens

<400> 131
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt aatcttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagcgg 300
gatagcagtg gctggtacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 132
<211> 123
<212> PRT
<213> Homo sapiens

<400> 132
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu Ile Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Arg Asp Ser Ser Gly Trp Tyr Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 133
<211> 321
<212> DNA
<213> Homo sapiens

<400> 133
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcctccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtcgatc tgggacagaa ttcaccctca caatcagcag cctgcagcct 240
gaagattttg caagttatta ctgtctacag cataggagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 134
<211> 107
<212> PRT
<213> Homo sapiens

<400> 134
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Arg Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Ser Tyr Tyr Cys Leu Gln His Arg Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 135
<211> 345
<212> DNA
<213> Homo sapiens

<400> 135
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt atttatagcg gtggtagcac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aggcgaagga 300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca 345

<210> 136
<211> 115
<212> PRT
<213> Homo sapiens

<400> 136
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Gly Glu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110
Val Ser Ser
        115
```

<210> 137
<211> 321
<212> DNA
<213> Homo sapiens

<400> 137
gaaatagtga tgacgcagtc tccatccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccatca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag tacactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcaacag tataataact ggccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 138
<211> 107
<212> PRT
<213> Homo sapiens

<400> 138
```
Glu Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Val Ser Pro Gly
 1                  5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Gly Ala Ser Ile Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Phe
                85                  90                  95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105
```

<210> 139
<211> 348
<212> DNA
<213> Homo sapiens

<400> 139
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagaa gtggtagtac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatcttta 300
ggcggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctca 348

<210> 140
<211> 116
<212> PRT
<213> Homo sapiens

<400> 140
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110
Thr Val Ser Ser
115

<210> 141
<211> 321
<212> DNA
<213> Homo sapiens

<400> 141
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcgcc 60
atcacttgcc ggacaagtca gagcattagc agttatttaa attggtatca gcagaaacca 120
gggaaagccc ctgagctcct gatctatgct gcatccaatt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttccagta ccctcatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 142
<211> 107
<212> PRT
<213> Homo sapiens

<400> 142
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Ala Ile Thr Cys Arg Thr Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Leu Ile
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 143
<211> 345

<212> DNA
<213> Homo sapiens

<400> 143
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactacg tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt atttataacg ctggtagcgc gtactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtttctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aggaactggg 300
gcctttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 144
<211> 115
<212> PRT
<213> Homo sapiens

<400> 144
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Val Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Asn Ala Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Thr Gly Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ser
115

<210> 145
<211> 321
<212> DNA
<213> Homo sapiens

<400> 145
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccagactcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtaggac tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataact ggcctctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 146
<211> 107
<212> PRT
<213> Homo sapiens

<400> 146
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

```
    50                  55                  60
Ser Arg Thr Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 147
<211> 348
<212> DNA
<213> Homo sapiens

<400> 147
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagaa gtggtagtac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatcttta 300
ggcggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctca 348

<210> 148
<211> 116
<212> PRT
<213> Homo sapiens

<400> 148
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110
Thr Val Ser Ser
        115
```

<210> 149
<211> 321
<212> DNA
<213> Homo sapiens

<400> 149
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc ggacaagtca gagcattagc agctatttaa actggtatca ccagaaacca 120
gggaaagccc ctgagctcct gatctatgct gcattcaatt tacaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttccagta ccctcatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 150
<211> 107

<212> PRT
<213> Homo sapiens

<400> 150
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Glu Leu Leu Ile
35 40 45
Tyr Ala Ala Phe Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Leu Ile
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 151
<211> 345
<212> DNA
<213> Homo sapiens

<400> 151
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt atttatagcg gtggtagcac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aggcgaagga 300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca 345

<210> 152
<211> 115
<212> PRT
<213> Homo sapiens

<400> 152
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Glu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110
Val Ser Ser
115

<210> 153
<211> 324
<212> DNA
<213> Homo sapiens

<400> 153
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60
acctgctctg gagatgcatt gccaaaaaaa tatgtttatt ggtaccagca gaagtcaggc 120
caggcccctg tgctggtcat ctatgaggac agcaaacgac cctccgggat ccctgagaga 180
ttctctggct ccagctcagg gacaatggcc accttgacta tcaatggggc ccaggtggag 240
gatgaagctg actactactg ttactcaacg gacagcagtg gtaatcatgt ggtattcggc 300
ggagggacca agctgaccgt ccta 324

<210> 154
<211> 108
<212> PRT
<213> Homo sapiens

<400> 154
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Val
20 25 30
Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Asn Gly Ala Gln Val Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Ser Gly Asn His
85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 155
<211> 321
<212> DNA
<213> Homo sapiens

<400> 155
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc ggacaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctgaggtcct gatctatgct gcatccaatt tgcaacgtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttccagta ccctcatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 156
<211> 107
<212> PRT
<213> Homo sapiens

<400> 156
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Val Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Leu Ile

85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 157
<211> 369
<212> DNA
<213> Homo sapiens

<400> 157
gaggtgcagc tggtggagtc tgggggaggc ctggtcaagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatct attagtagta gtagtagtta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagggggggt 300
ataactggaa ctacgaacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 158
<211> 123
<212> PRT
<213> Homo sapiens

<400> 158
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Ile Thr Gly Thr Thr Asn Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 159
<211> 321
<212> DNA
<213> Homo sapiens

<400> 159
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc ggacaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctgaactcct gatctatgct gcatttaatt tgcaaagtgg ggtcccatca 180
aggatcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaccct 240
gaagattttg caacttacta ctgtcaacag agttccagta ccctcatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 160
<211> 107
<212> PRT
<213> Homo sapiens

<400> 160
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Leu Leu Ile
35 40 45
Tyr Ala Ala Phe Asn Leu Gln Ser Gly Val Pro Ser Arg Ile Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu His Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Leu Ile
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 161
<211> 375
<212> DNA
<213> Homo sapiens

<400> 161
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc ggctactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggtgg cacaaactat 180
gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagccccc 300
ctctggacgg tacgtagctg gtactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 162
<211> 125
<212> PRT
<213> Homo sapiens

<400> 162
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ala Pro Leu Trp Thr Val Arg Ser Trp Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 163
<211> 330
<212> DNA
<213> Homo sapiens

<400> 163

cagtctgtat tgacgcagcc gccctcaatg tctgcggccc caggacagaa ggtcaccatc 60
tcctgctctg gaagcagctc caacattggg aataattatg tatcctggta ccagcagctc 120
ccaggaatag cccccaaact cctcatttat gacaataata agcgaccctc agggattcct 180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag 240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgctggggtg 300
ttcggcggag ggaccaagct gaccgtccta 330

<210> 164
<211> 110
<212> PRT
<213> Homo sapiens

<400> 164
Gln Ser Val Leu Thr Gln Pro Pro Ser Met Ser Ala Ala Pro Gly Gln
1 5 10 15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Ile Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65 70 75 80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
85 90 95
Ser Ala Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 165
<211> 348
<212> DNA
<213> Homo sapiens

<400> 165
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaaga cttctgaata cagctttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcttg gtgactcaga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag taccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagaagtaac 300
tggggtcttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 166
<211> 116
<212> PRT
<213> Homo sapiens

<400> 166
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Thr Ser Glu Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Leu Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Ser Asn Trp Gly Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110
Thr Val Ser Ser
115

<210> 167
<211> 333
<212> DNA
<213> Homo sapiens

<400> 167
cagtctgtgc tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60
tcctgcactg ggagcagttc caacatcggg gcaggttatg atgtacactg gtaccagcag 120
tttccaggaa cagcccccaa actcctcatc caaggtaaca gcaatcggcc ctcaggggtc 180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240
caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300
gtgttcggcg gagggaccaa gctgaccgtc ctt 333

<210> 168
<211> 111
<212> PRT
<213> Homo sapiens

<400> 168
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Gln Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 169
<211> 351
<212> DNA
<213> Homo sapiens

<400> 169
caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacg ttctatagta tcacctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgataa cacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaacgttt 300
accagtggct ttgactactg gggccaggga accctggtca ccgtctcctc a 351

<210> 170
<211> 117
<212> PRT
<213> Homo sapiens

<400> 170
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Phe Tyr
            20                  25                  30
Ser Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Ser Ala Tyr Asn Asp Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Thr Phe Thr Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser
        115
```

<210> 171
<211> 324
<212> DNA
<213> Homo sapiens

<400> 171
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaaggtat tatgcaagct ggtaccagca gaagccagga 120
caggccccta tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taactcccgg gacagcagtg gtaaccatct ggtgttcggc 300
ggagggacca agctgaccgt ccta 324

<210> 172
<211> 108
<212> PRT
<213> Homo sapiens

<400> 172

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1                  5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Arg Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
                85                  90                  95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 173
<211> 375
<212> DNA
<213> Homo sapiens

<400> 173
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt taccttcagt agttatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaataccat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaat 300
actatggttc ggggggggga ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 174
<211> 125
<212> PRT
<213> Homo sapiens

<400> 174

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5				10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Asp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	His	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Asn	Thr	Met	Val	Arg	Gly	Gly	Asp	Tyr	Tyr	Tyr	Gly	Met
			100					105					110		
Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
		115					120					125			

<210> 175
<211> 321
<212> DNA
<213> Homo sapiens

<400> 175
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
aggaaagccc ctaagcgcct gatctttgct gcgtccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 176
<211> 107
<212> PRT
<213> Homo sapiens

<400> 176

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp
			20					25					30		
Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Arg	Lys	Ala	Pro	Lys	Arg	Leu	Ile
		35					40					45			
Phe	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Pro	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	His	Asn	Ser	Tyr	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 177
<211> 354
<212> DNA
<213> Homo sapiens

<400> 177
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat ttctattaca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgaggt ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agataggttt 300
accagtggct ggtttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 178
<211> 118
<212> PRT
<213> Homo sapiens

<400> 178
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Phe Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Asp Arg Phe Thr Ser Gly Trp Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 179
<211> 321
<212> DNA
<213> Homo sapiens

<400> 179
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
aggaaagccc ctaagcgcct gatctttgct gcgtccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 180
<211> 107
<212> PRT
<213> Homo sapiens

<400> 180
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp

```
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Arg Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 181
<211> 345
<212> DNA
<213> Homo sapiens

<400> 181
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt aacaactaca tgcactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt atttatagcg gtggtaacac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctatttctt 240
caaatgaaca gcctgaaaac cgaggacacg gccgtgtatt actgtgcgag aggtcccggg 300
gcttttgata tctggggcca agggacaatg gtcaccgtct cttca 345

<210> 182
<211> 115
<212> PRT
<213> Homo sapiens

<400> 182
```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Asn Asn
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Tyr Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Gly Pro Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
            100                 105                 110
Val Ser Ser
        115
```

<210> 183
<211> 321
<212> DNA
<213> Homo sapiens

<400> 183
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagtcacc 60
ctctcctgca gggccagtca gagtgctacc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
agattcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataact ggcctttcac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> 184
<211> 107
<212> PRT
<213> Homo sapiens

<400> 184
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser Ala Thr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Phe
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 185
<211> 345
<212> DNA
<213> Homo sapiens

<400> 185
gaggtgcagc tggtggagtc tggaggaggc ttgatccagc ctgggggtc cctgagactc 60
tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagttgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt atttatagcg gtggtagcac atactacgca 180
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aggtcccggg 300
gcttttgata tctggggcca agggacaatg gtcaccgtct cttca 345

<210> 186
<211> 115
<212> PRT
<213> Homo sapiens

<400> 186
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Gly Pro Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
100 105 110
Val Ser Ser
115

<210> 187
<211> 327
<212> DNA
<213> Homo sapiens

<400> 187
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtttca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccaatt ttctaagtgg ggtcccatca 180
aggttcagcg gcagtggctc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagatttta caacttatta ctgtctacag cataatcctt accctccgag gctcactttc 300
ggcggaggga ccaaggtaga gatcaaa 327

<210> 188
<211> 109
<212> PRT
<213> Homo sapiens

<400> 188
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Phe Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Thr Thr Tyr Tyr Cys Leu Gln His Asn Pro Tyr Pro Pro
85 90 95
Arg Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 189
<211> 363
<212> DNA
<213> Homo sapiens

<400> 189
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300
gactacggtg gtaaccctta ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 190
<211> 121
<212> PRT
<213> Homo sapiens

<400> 190
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Gly Asp Tyr Gly Gly Asn Pro Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 191
<211> 324
<212> DNA
<213> Homo sapiens

<400> 191
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaagctat tatgcaagct ggtaccagca gaagccagga 120
caggcccctg tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcaga aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taagtcccgg gacagcagtt ttaaccatct ggtattcggc 300
ggagggacca agttgaccgt ccta 324

<210> 192
<211> 108
<212> PRT
<213> Homo sapiens

<400> 192

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Glu Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ser Ser Phe Asn His
                85                  90                  95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 193
<211> 363
<212> DNA
<213> Homo sapiens

<400> 193
caggtgcacc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggcatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtac aagagagggg 300
gactacggtg gttaccctta ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 194
<211> 121
<212> PRT
<213> Homo sapiens

<400> 194
Gln Val His Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg Glu Gly Asp Tyr Gly Gly Tyr Pro Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 195
<211> 324
<212> DNA
<213> Homo sapiens

<400> 195
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacatcct cagaagctat tatgcaagct ggtaccagca gaagccagga 120
caggcccctg tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taagtcccgg gacagcagtt ataaccatct ggtattcggc 300
ggagggacca aactgaccgt ccta 324

<210> 196
<211> 108
<212> PRT
<213> Homo sapiens

<400> 196
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ile Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ser Ser Tyr Asn His
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 197
<211> 366

<212> DNA
<213> Homo sapiens

<400> 197
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcaatt atatggtatg atggaagtaa tgaatactat 180
ggagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatccc 300
ctccgtatag tagtggctgg ggactttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca 366

<210> 198
<211> 122
<212> PRT
<213> Homo sapiens

<400> 198
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ile Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Gly Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Pro Leu Arg Ile Val Val Ala Gly Asp Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 199
<211> 333
<212> DNA
<213> Homo sapiens

<400> 199
cagtctgtgc tgacgcagcc gccctcagtg tctggggccc cagggctgag ggtcaccatc 60
tcctgcactg gaaacagctc caacatcggg gcaggttatg atgtacactg gtaccagcag 120
cttccaggaa cagcccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240
caggctgagg atgagactga ttattactgc cagtcctatg acagcagcct gagtggttcg 300
gtattcggcg gagggaccaa gctgaccgtc cta 333

<210> 200
<211> 111
<212> PRT
<213> Homo sapiens

<400> 200
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Leu
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Asn Ser Ser Asn Ile Gly Ala Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

```
Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Thr Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 201
<211> 363
<212> DNA
<213> Homo sapiens

<400> 201
caggtgcacc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggcatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtac aagagagggg 300
gactacggtg gttaccctta ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 202
<211> 121
<212> PRT
<213> Homo sapiens

<400> 202
```
Gln Val His Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Thr Arg Glu Gly Asp Tyr Gly Gly Tyr Pro Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 203
<211> 324
<212> DNA
<213> Homo sapiens

<400> 203
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacatcct cagaagctat tatgcaagct ggtaccagca gaagccagga 120
caggccccta tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
gatgaggctg actattactg taagtcccgg gacagcagtt ataaccatct ggtattcggc 300
ggagggacca aactgaccgt ccta 324

<210> 204
<211> 108
<212> PRT
<213> Homo sapiens

<400> 204
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ile Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ser Ser Tyr Asn His
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 205
<211> 375
<212> DNA
<213> Homo sapiens

<400> 205
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagact 300
acggtgacta aggagggcta ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 206
<211> 125
<212> PRT
<213> Homo sapiens

<400> 206
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Thr Val Thr Lys Glu Gly Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 207

<211> 321
<212> DNA
<213> Homo sapiens

<400> 207
gacatccaga tgacccagtc tccatcttcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 208
<211> 107
<212> PRT
<213> Homo sapiens

<400> 208
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 209
<211> 360
<212> DNA
<213> Homo sapiens

<400> 209
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctatat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagatcccgc 300
tacggtgact gggggtggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 210
<211> 120
<212> PRT
<213> Homo sapiens

<400> 210
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val

```
     50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Arg Tyr Gly Asp Trp Gly Trp Phe Asp Pro Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 211
<211> 330
<212> DNA
<213> Homo sapiens

<400> 211
cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60
tcttgttctg gaagcagctc caacatcgga agtaatactg taaactggta ccagcagctc 120
ccaggaacgg cccccaaact cctcatctat agtaataatc agcggccctc aggggtccct 180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 240
tctgaggatg aggctgatta ttactgtgca gcatgggatg acagcctgaa tggtccggtg 300
ttcggcggag ggaccaagct gaccgtccta 330

<210> 212
<211> 110
<212> PRT
<213> Homo sapiens

<400> 212
```
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95
Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 213
<211> 366
<212> DNA
<213> Homo sapiens

<400> 213
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcaatt atatggtatg atggaagtaa tgaatactat 180
ggagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatccc 300
ctccgtatag tagtggctgg ggactttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca 366

<210> 214

<211> 122
<212> PRT
<213> Homo sapiens

<400> 214
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ile Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Gly Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Pro Leu Arg Ile Val Val Ala Gly Asp Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 215
<211> 321
<212> DNA
<213> Homo sapiens

<400> 215
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttatc agcaacttag cctggtacca gcagcaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tttcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataact ggccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 216
<211> 107
<212> PRT
<213> Homo sapiens

<400> 216
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ile Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Gln Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Phe Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 217
<211> 375
<212> DNA

<213> Homo sapiens

<400> 217
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagact 300
acggtgacta aggagggcta ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 218
<211> 125
<212> PRT
<213> Homo sapiens

<400> 218
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Thr Val Thr Lys Glu Gly Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 219
<211> 321
<212> DNA
<213> Homo sapiens

<400> 219
gacatccaga tgacccagtc tccatcttcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 220
<211> 107
<212> PRT
<213> Homo sapiens

<400> 220
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

```
     50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 221
<211> 375
<212> DNA
<213> Homo sapiens

<400> 221
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatgaca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcaatt atatcatatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagagaat 300
gcggtgactt acgggggcta ctaccactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 222
<211> 125
<212> PRT
<213> Homo sapiens

<400> 222
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Ile Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Asn Ala Val Thr Tyr Gly Gly Tyr Tyr His Tyr Gly Met
            100                 105                 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 223
<211> 321
<212> DNA
<213> Homo sapiens

<400> 223
gacatccaga tgacccagtc tccatcctcc ctgtctacat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 224

<211> 107
<212> PRT
<213> Homo sapiens

<400> 224
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 225
<211> 375
<212> DNA
<213> Homo sapiens

<400> 225
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtacaa catctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atctggtatg atggaagtat taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaag 300
gattgtggtg gtgactgtta cagccactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 226
<211> 125
<212> PRT
<213> Homo sapiens

<400> 226
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Lys Asp Cys Gly Gly Asp Cys Tyr Ser His Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 227
<211> 321

<212> DNA
<213> Homo sapiens

<400> 227
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacgtatta ctgtctacag catatgagtc tcccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 228
<211> 107
<212> PRT
<213> Homo sapiens

<400> 228
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Met Ser Leu Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 229
<211> 375
<212> DNA
<213> Homo sapiens

<400> 229
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtacaa catctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atctggtatg atggaagtat taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaag 300
gattgtggtg gtgactgtta cagccactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 230
<211> 125
<212> PRT
<213> Homo sapiens

<400> 230
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Val Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Lys Asp Cys Gly Gly Asp Cys Tyr Ser His Tyr Gly Met
            100                 105                 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 231
<211> 321
<212> DNA
<213> Homo sapiens

<400> 231
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacgtatta ctgtctacag catatgagtc tcccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 232
<211> 107
<212> PRT
<213> Homo sapiens

<400> 232
```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Met Ser Leu Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 233
<211> 375
<212> DNA
<213> Homo sapiens

<400> 233
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtacaa catctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atctggtatg atggaagtat taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaag 300
gattgtggtg gtgactgtta cagccactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 234
<211> 125

<212> PRT
<213> Homo sapiens

<400> 234
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Lys Asp Cys Gly Gly Asp Cys Tyr Ser His Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 235
<211> 321
<212> DNA
<213> Homo sapiens

<400> 235
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacgtatta ctgtctacag catatgagtc tcccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 236
<211> 107
<212> PRT
<213> Homo sapiens

<400> 236
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Met Ser Leu Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 237
<211> 375
<212> DNA
<213> Homo sapiens

<400> 237
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtacaa catctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atctggtatg atggaagtat taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagaag 300
gattgtggtg gtgactgtta cagccactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

<210> 238
<211> 125
<212> PRT
<213> Homo sapiens

<400> 238
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Lys Asp Cys Gly Gly Asp Cys Tyr Ser His Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 239
<211> 321
<212> DNA
<213> Homo sapiens

<400> 239
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacgtatta ctgtctacag catatgagtc tcccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 240
<211> 107
<212> PRT
<213> Homo sapiens

<400> 240
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

```
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Met Ser Leu Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 241
<211> 366
<212> DNA
<213> Homo sapiens

<400> 241
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagaaa taaatacaat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgaat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattta 300
acgtattacg atattttggg cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 242
<211> 122
<212> PRT
<213> Homo sapiens

<400> 242
```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Tyr Asn Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Leu Thr Tyr Tyr Asp Ile Leu Gly Gly Met Asp Val Trp
            100                 105                 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 243
<211> 321
<212> DNA
<213> Homo sapiens

<400> 243
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccggggga aagagccacc 60
ctctcctgca gggccagtca gagtgttacc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagaa ttcactctca ccatcagcag cctgccgtct 240
gaagattttg cagtttatta ctgtcagcag tatcatacct ggccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 244
<211> 107

<212> PRT
<213> Homo sapiens

<400> 244
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Pro Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr His Thr Trp Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 245
<211> 366
<212> DNA
<213> Homo sapiens

<400> 245
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagaaa taaatacaat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgaat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattta 300
acgtattacg atattttggg cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 246
<211> 122
<212> PRT
<213> Homo sapiens

<400> 246
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Tyr Asn Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Thr Tyr Tyr Asp Ile Leu Gly Gly Met Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 247
<211> 321
<212> DNA

<213> Homo sapiens

<400> 247
gaaatagtga tgacgcagtc tccatccacc ctgtctgtgt ctccggggga aagagccacc 60
ctctcctgca gggccagtca gagtgttacc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagaa ttcactctca ccatcagcag cctgccgtct 240
gaagattttg cagtttatta ctgtcagcag tatcatacct ggccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 248
<211> 107
<212> PRT
<213> Homo sapiens

<400> 248
Glu Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Pro Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr His Thr Trp Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 249
<211> 366
<212> DNA
<213> Homo sapiens

<400> 249
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagaaa taaatacaat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgaat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattta 300
acgtattacg atattttggg cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 250
<211> 122
<212> PRT
<213> Homo sapiens

<400> 250
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Tyr Asn Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Thr Tyr Tyr Asp Ile Leu Gly Gly Met Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 251
<211> 321
<212> DNA
<213> Homo sapiens

<400> 251
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga catgatttag gctggtatca gcagaaacca 120
gggaaagccc ctgagcgcct gatctatggt gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 252
<211> 107
<212> PRT
<213> Homo sapiens

<400> 252
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg His Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Arg Leu Ile
35 40 45
Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 253
<211> 402
<212> DNA
<213> Homo sapiens

<400> 253
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtg atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggtaat 300
cgcgtagtag tggctggtac gagggtaact cccgctaact ggggatacta ctattacgga 360
atggacgtct ggggccaagg gaccacggtc accgtctcct ca 402

<210> 254
<211> 134
<212> PRT

<213> Homo sapiens

<400> 254

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Asn Arg Val Val Val Ala Gly Thr Arg Val Thr Pro Ala
            100                 105                 110
Asn Trp Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
        115                 120                 125
Thr Val Thr Val Ser Ser
    130
```

<210> 255
<211> 321
<212> DNA
<213> Homo sapiens

<400> 255

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagtgcct gatctatgtt gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a                                           321
```

<210> 256
<211> 107
<212> PRT
<213> Homo sapiens

<400> 256

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile
        35                  40                  45
Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 257
<211> 348
<212> DNA

<213> Homo sapiens

<400> 257
gaggtgcaac tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt aattatggca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac ataagtaata gtattacttc caaatactac 180
gctgactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ttcactgtat 240
ctgcaaatga acagcctgag agacgtggac acggctgtgt atcactgtgc gagaggaccg 300
ggcgggtttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 258
<211> 116
<212> PRT
<213> Homo sapiens

<400> 258
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Asn Ser Ile Thr Ser Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Asp Val Asp Thr Ala Val Tyr His Cys
85 90 95
Ala Arg Gly Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 259
<211> 321
<212> DNA
<213> Homo sapiens

<400> 259
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc cgaagtgcct gatctatgtt gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 260
<211> 107
<212> PRT
<213> Homo sapiens

<400> 260
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile
35 40 45
Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

```
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 261
<211> 366
<212> DNA
<213> Homo sapiens

<400> 261
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc cgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattac 300
tatgatagta gtggttatca tccttttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca 366

<210> 262
<211> 122
<212> PRT
<213> Homo sapiens

<400> 262
```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Asp Tyr Tyr Asp Ser Ser Gly Tyr His Pro Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 263
<211> 321
<212> DNA
<213> Homo sapiens

<400> 263
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca gggcattagc aattatttag cctggtatca acagaaacca 120
gggaaagttc ctaagttcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccgtcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaatg tataacagtg tcccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 264
<211> 107

<212> PRT
<213> Homo sapiens

<400> 264
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Met Tyr Asn Ser Val Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 265
<211> 157
<212> PRT
<213> homo sapiens

<400> 265
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala
85 90 95
Ile Lys Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 266
<211> 156
<212> PRT
<213> Mus musculus

<400> 266
Leu Arg Ser Ser Ser Gln Asn Ser Ser Asp Lys Pro Val Ala His Val
1 5 10 15
Val Ala Asn His Gln Val Glu Glu Gln Leu Glu Trp Leu Ser Gln Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Met Asp Leu Lys Asp Asn Gln Leu
35 40 45
Val Val Pro Ala Asp Gly Leu Tyr Leu Val Tyr Ser Gln Val Leu Phe

```
    50                  55                  60
Lys Gly Gln Gly Cys Pro Asp Tyr Val Leu Leu Thr His Thr Val Ser
65                  70                  75                  80
Arg Phe Ala Ile Ser Tyr Gln Glu Lys Val Asn Leu Leu Ser Ala Val
                85                  90                  95
Lys Ser Pro Cys Pro Lys Asp Thr Pro Glu Gly Ala Glu Leu Lys Pro
            100                 105                 110
Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly
        115                 120                 125
Asp Gln Leu Ser Ala Glu Val Asn Leu Pro Lys Tyr Leu Asp Phe Ala
    130                 135                 140
Glu Ser Gly Gln Val Tyr Phe Gly Val Ile Ala Leu
145                 150                 155


<210> 267
<211> 109
<212> PRT
<213> Homo sapiens

<400> 267
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1                  5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105


<210> 268
<211> 108
<212> PRT
<213> Homo sapiens

<400> 268
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
 1                  5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
            20                  25                  30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105


<210> 269
<211> 109
```

<212> PRT
<213> Homo sapiens

<400> 269
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 270
<211> 109
<212> PRT
<213> Homo sapiens

<400> 270
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 271
<211> 108
<212> PRT
<213> Homo sapiens

<400> 271
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser

100 105

<210> 272
<211> 110
<212> PRT
<213> Homo sapiens

<400> 272
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105 110

<210> 273
<211> 107
<212> PRT
<213> Homo sapiens

<400> 273
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 274
<211> 107
<212> PRT
<213> Homo sapiens

<400> 274
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

```
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 275
<211> 114
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 101, 102
<223> Xaa = Any Amino Acid

<400> 275

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1               5                  10                  15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
            20                  25                  30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45
Pro Arg Arg Leu Ile Tyr Lys Val Trp Asn Trp Asp Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95
Thr His Trp Pro Xaa Xaa Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
            100                 105                 110
Ile Lys
```

<210> 276
<211> 111
<212> PRT
<213> Homo sapiens

<400> 276

```
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1               5                  10                  15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95
Leu Gln Thr Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 277
<211> 106

<212> PRT
<213> Homo sapiens

<400> 277
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Trp Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 278
<211> 109
<212> PRT
<213> Homo sapiens

<400> 278
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 279
<211> 109
<212> PRT
<213> Homo sapiens

<400> 279
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

100 105

<210> 280
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 98
<223> Xaa = Any Amino Acid

<400> 280
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Xaa Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 281
<211> 109
<212> PRT
<213> Homo sapiens

<400> 281
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 282
<211> 108
<212> PRT
<213> Homo sapiens

<400> 282
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn

```
            20                  25                  30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
            100                 105
```

<210> 283
<211> 109
<212> PRT
<213> Homo sapiens

<400> 283

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
```

<210> 284
<211> 109
<212> PRT
<213> Homo sapiens

<400> 284

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 285
<211> 109
<212> PRT
<213> Homo sapiens

<400> 285
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 286
<211> 108
<212> PRT
<213> Homo sapiens

<400> 286
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 287
<211> 109
<212> PRT
<213> Homo sapiens

<400> 287
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 288
<211> 109
<212> PRT
<213> Homo sapiens

<400> 288
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 289
<211> 109
<212> PRT
<213> Homo sapiens

<400> 289
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 290
<211> 109
<212> PRT
<213> Homo sapiens

<400> 290
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

```
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 291
<211> 109
<212> PRT
<213> Homo sapiens

<400> 291

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 292
<211> 109
<212> PRT
<213> Homo sapiens

<400> 292

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
```

<210> 293
<211> 109
<212> PRT
<213> Homo sapiens

<400> 293

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

```
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
```

<210> 294
<211> 109
<212> PRT
<213> Homo sapiens

<400> 294

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1                  5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 295
<211> 108
<212> PRT
<213> Homo sapiens

<400> 295

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1                  5                  10                  15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 296
<211> 109
<212> PRT
<213> Homo sapiens

<400> 296

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 297
<211> 108
<212> PRT
<213> Homo sapiens

<400> 297

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
            20                  25                  30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105
```

<210> 298
<211> 109
<212> PRT
<213> Homo sapiens

<400> 298

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105
```

<210> 299

<211> 109
<212> PRT
<213> Homo sapiens

<400> 299
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 300
<211> 108
<212> PRT
<213> Homo sapiens

<400> 300
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 301
<211> 109
<212> PRT
<213> Homo sapiens

<400> 301
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 302
<211> 109
<212> PRT
<213> Homo sapiens

<400> 302
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 303
<211> 109
<212> PRT
<213> Homo sapiens

<400> 303
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 304
<211> 111
<212> PRT
<213> Homo sapiens

<400> 304
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe

```
    50                  55                  60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 305
<211> 107
<212> PRT
<213> Homo sapiens

<400> 305

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 306
<211> 107
<212> PRT
<213> Homo sapiens

<400> 306

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Phe
                85                  90                  95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105
```

<210> 307
<211> 107
<212> PRT
<213> Homo sapiens

<400> 307

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
```

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 308
<211> 107
<212> PRT
<213> Homo sapiens

<400> 308

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
                85                  90                  95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105
```

<210> 309
<211> 110
<212> PRT
<213> Homo sapiens

<400> 309

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65                  70                  75                  80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
                85                  90                  95
Ser Ala Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 310
<211> 107
<212> PRT

<213> Homo sapiens

<400> 310

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Ile
                85                  90                  95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105
```

<210> 311
<211> 110
<212> PRT
<213> Homo sapiens

<400> 311

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65                  70                  75                  80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
                85                  90                  95
Ser Ala Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 312
<211> 107
<212> PRT
<213> Homo sapiens

<400> 312

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 313
<211> 107
<212> PRT
<213> Homo sapiens

<400> 313
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 314
<211> 107
<212> PRT
<213> Homo sapiens

<400> 314
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 315
<211> 110
<212> PRT
<213> Homo sapiens

<400> 315
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30
Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln

65 70 75 80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95
Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 316
<211> 108
<212> PRT
<213> Homo sapiens

<400> 316
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 317
<211> 108
<212> PRT
<213> Homo sapiens

<400> 317
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
20 25 30
Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Ser Gly Asn His
85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 318
<211> 107
<212> PRT
<213> Homo sapiens

<400> 318
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

```
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Ile
                85                  90                  95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105
```

<210> 319
<211> 108
<212> PRT
<213> Homo sapiens

<400> 319

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
                85                  90                  95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 320
<211> 111
<212> PRT
<213> Homo sapiens

<400> 320

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45
Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95
Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```